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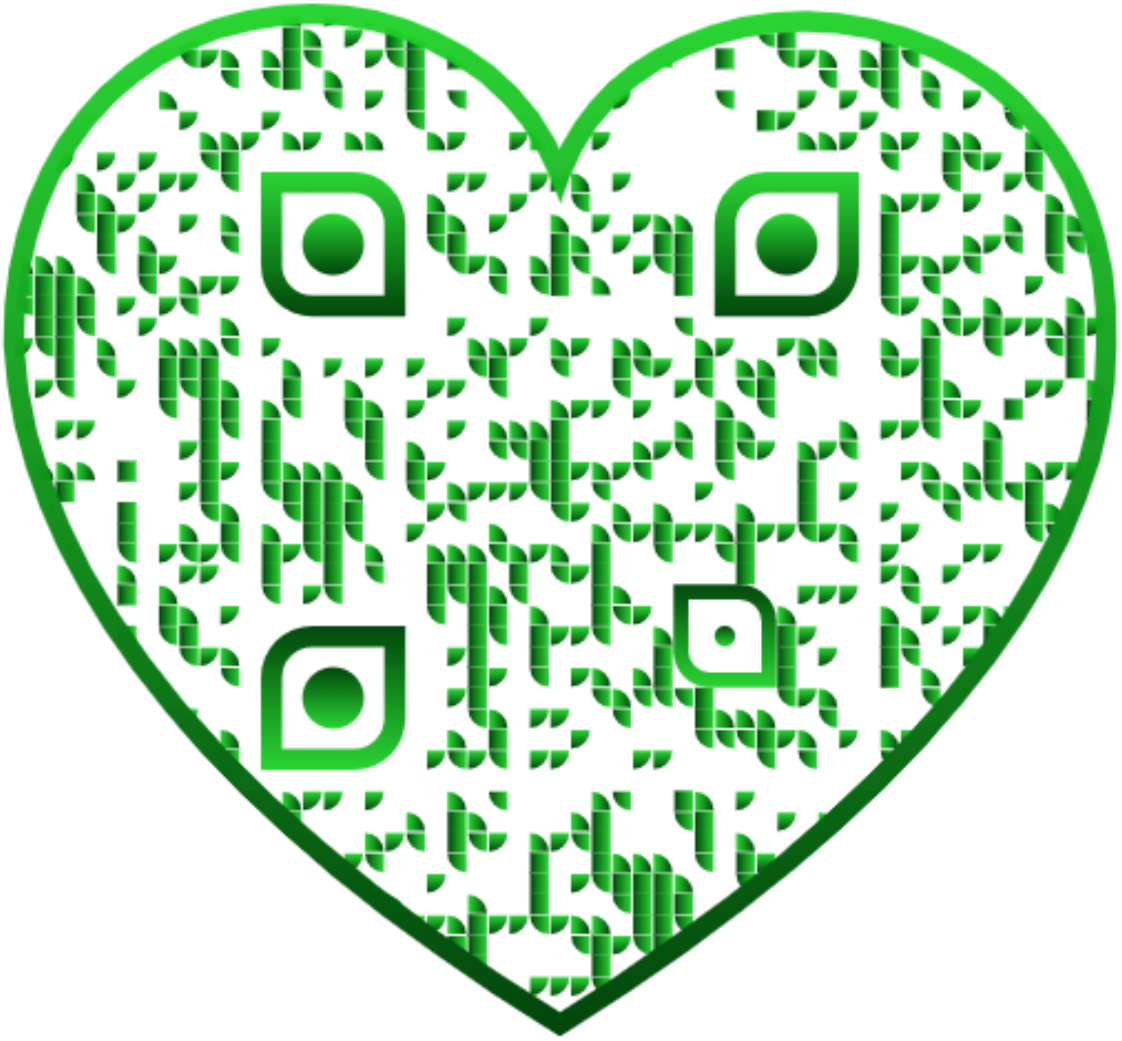

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أقسم بالله أني لن أخون الكاتب و لن أنشر فيديوهاته أو أسمح لأحد غيري بالوصول اليها على حسابي أو مشاهداتها بجواري بأي طريقه...

أي طبيب زميل محتاج الكتاب ولا يملك سعرة لا يتردد بالتواصل ٠١٠٠٤٤٨٦١٨٨

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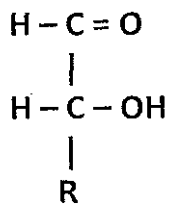
CHAPTER 1

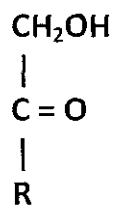
Carbohydrates Chemistry

CARBOHYDRATES

❖ **Definition:** - are organic substances composed of carbon, hydrogen, and oxygen.
Or - are **simple sugar** (polyhydroxy aldehyde or ketone) or its **derivatives**.
الكربوهيدرات هي: السكر البسيط وأي من مشتقاته
السكر البسيط هو: الألدهيدات أو الكيتونات عديدة الهيدروكسيل



Polyhydroxyaldehydes



Polyhydroxyketones

❖ **Classification of carbohydrates:** according to the **hydrolysis** (تحلل مائي) products

1. Monosaccharides	Contain 1 sugar unit. (Can't be Hydrolyzed)
2. Disaccharides	Contain 2 sugar units.
3. Oligosaccharide	Contain 3-10 sugar units.
4. Polysaccharides	Contain more than 10 sugar units.

N.B. Usually the ratio between Carbon & H_2O is 1. Hence the name carbohydrate.

Monosaccharides (glycoses)

❖ **Definition:** They are the **simplest units** of carbohydrate containing **one** sugar unit.
General formula is: $C_n(H_2O)_n$.

❖ **Naming of monosaccharides:**

A. According to the Functional group:

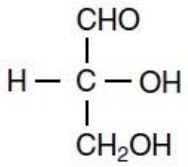
1. **Aldoses:** monosaccharides containing aldehyde group (-CHO).
2. **Ketoses:** monosaccharides containing ketone group (-C=O).

B. According to the No. of Carbon atoms:

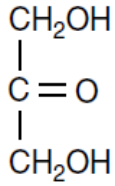
Sugar	No. of Carbons	Includes
Trioses	3	Aldotrioses and ketotrioses
Tetroses	4	Aldotetroses and ketotetroses
Pentoses	5	Aldopentoses and ketopentoses
Hexoses	6	Aldohexoses and ketohexoses

❖ Classification of monosaccharides:

1. **Trioses:** monosaccharides containing **3** carbons.
   a. **Aldotrioses:** Glyceraldehyde "glycerose".
   b. **Ketotrioses:** Dihydroxyacetone.

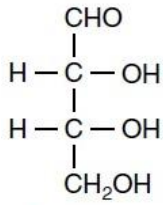


D-Glycerose
(D-glyceraldehyde)

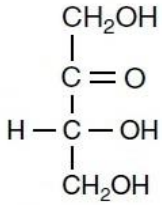


Dihydroxyacetone

2. **Tetroses:** **monosaccharides** containing **4** carbon atoms:
   a. **Note:** The suffix —ulose means Keto group.

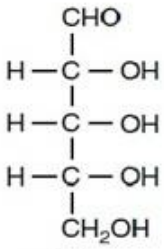


D-Erythrose

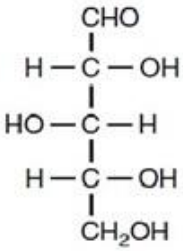


D-Erythrulose

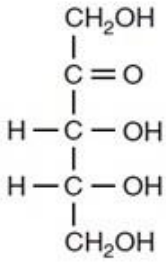
3. **Pentoses:** monosaccharides containing **5** carbon atoms.
   a. **Aldopentoses:** Ribose, arabinose, xylose and lyxose.
   b. **Ketopentoses:** Ribulose and xylulose.



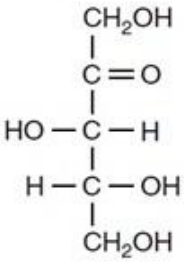
D-Ribose



D-Xylose



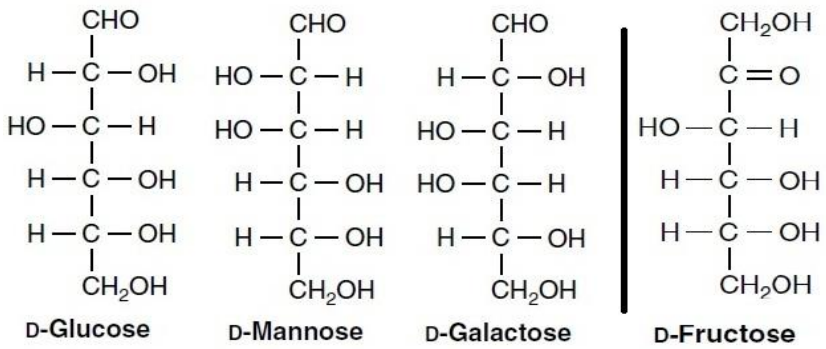
D-Ribulose



D-Xylulose

   c. **Importance (functions) of pentoses:**
      - **Ribose:**
        - Enter in the structure of nucleic acids (RNA and DNA.)
        - Enters in the structure of ATP, GTP .
        - Enters in the structure of coenzymes NAD, NADP and FAD.

4. **Hexoses:** monosaccharides containing **6** carbon atoms.
   a. **Aldohexoses:** glucose, mannose, and galactose.
   b. **Ketohexose:** fructose.



c. Importance (functions) of Hexoses:

1- **Glucose:** "grape sugar" is the most important sugar of carbohydrate:
- Glucose is the main sugar in blood
- Glucose is one of major sources of energy in the body.
- In the liver and other tissues, glucose is converted to all carbohydrates in the body e.g. glycogen, galactose,

2- **Galactose:**
- It can be converted into glucose in the liver.
- It is synthesized in mammary gland to make the lactose of milk (milk sugar)

3- **Fructose:** "fruit sugar":
- It can be converted into glucose in the liver.
- It is the main sugar of semen.

4- **Mannose:** A constituent of many glycoproteins.

❖ Properties of monosaccharides:

▪ Ring (cyclic) structure of sugars:

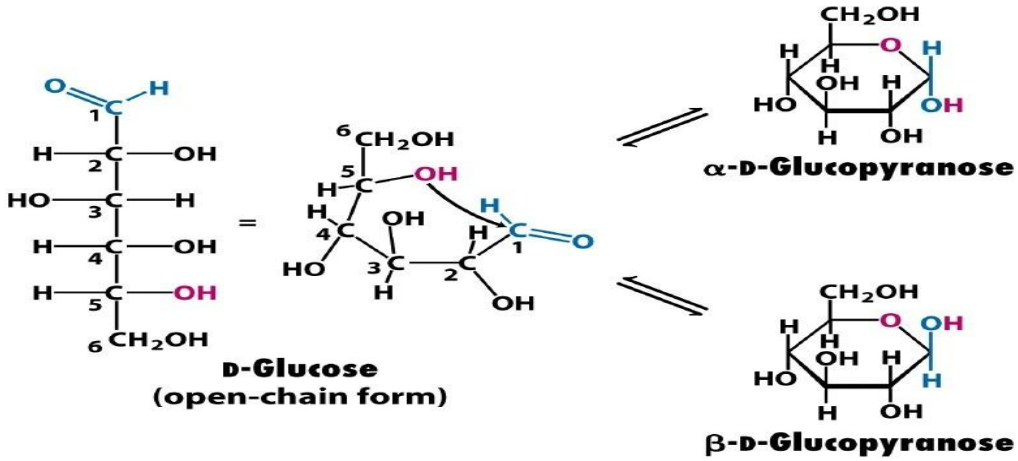
a) This Cyclic form is **due to:** reaction between C=O (carbonyl) of aldehyde group in Aldoses or of Ketol group in Ketoses with an alcoholic hydroxyl group to form
- **F**uranose → **4** Carbon ring
- **P**yranose → **5** Carbon ring

b) **If the remaining —OH** is on the **right** side, it is **α— sugar.**
If the remaining —OH is on the **left** side, it is **β — sugar.**

c) **Pyranose and furanose:**
- The 1-5 ring form is called pyranose as it resembles an Organic compound called pyran e.g. α and β glucopyranose.
- The 1-4 ring form is called furanose as it resembles an Organic compound called furan e.g. α and β glucofuranose.

Pyran

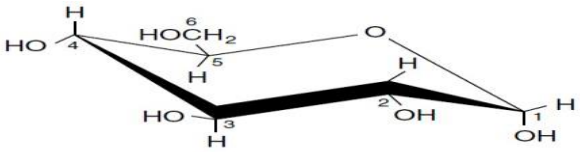
Furan



d) **Haworth and chair forms:**

i. Cyclic structure of sugars may be present in the form of Haworth or chair forms. as follows:

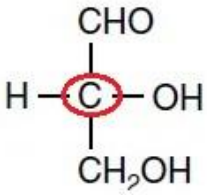
- All the **-OH** groups on the **right** side in old ring structure are written **downwards** in Haworth formula.
- All the **-OH** groups on the **left** side in old ring structure are written **upwards** in Haworth formula.
- These rules are reversed at CH2-OH groups **e.g.** last carbon atom of glucose that attached to oxygen i.e. c4 in furanose and C5 in pyranose.



D-Glucose. A: straight chain form.

Asymmetric carbon atom:

Is the carbon atom to which 4 different groups or atoms are attached.



Any substance containing asymmetric carbon atom shows 2 Properties,
Optical activity and Optical isomerism.

a. **Optical activity**: It is the ability of substance to rotate plane polarized light either to the right or to the left.

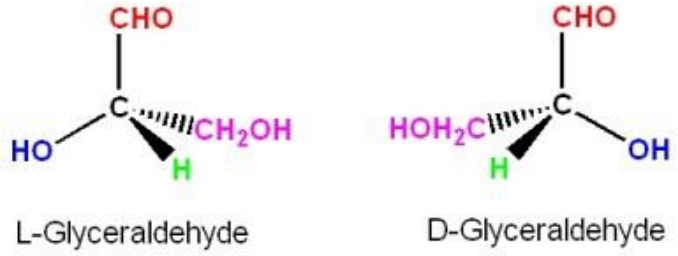
1- **If the substance rotates plane polarized light to the right so it is called**: dextrorotatory or d or **(+).**
2- **If it rotates it to the left so it is called:** levorotatory or l or **(-).**
3- **Glucose contains 4 asymmetric carbon atoms.** It is dextrorotatory, so it is sometimes named dextrose.
4- **Fructose contains 3 asymmetric carbon atoms**. It is levorotatory. so it is sometimes called: Levulose

b. Optical isomerism: It is the ability of substance to present in more than one form (isomer).

- Substance containing one asymmetric carbon atom has 2 isomers.

1- Configuration (Enantiomers): لازم كل الكربونات تكون معكوسة وابص ع اللي قبل الأخيرة

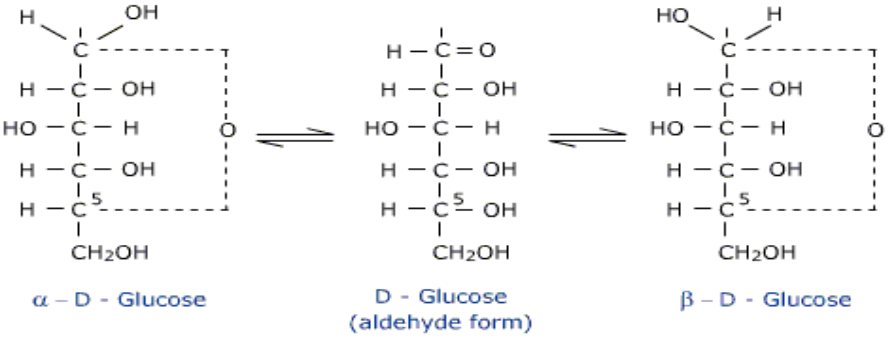
a. **The simplest carbohydrate is Glyceraldehyde** that has one asymmetric carbon atom. So it has 2 optically active forms.



2- Anomeric carbons & anomers: لازم السكر يكون في ال **ring structure**

a. **Anomeric carbon:** is the asymmetric carbon atom obtained from active carbonyl sugar group: **C_1** in **aldoses** and **C_2** in **ke toses**.

b. **Anomers:** These are isomers obtained from the change of position of hydroxyl group attached to the **anomeric carbon** e.g. **α** and **β glucose** are 2 anomers. Also **α** and **β fructose** are 2 anomers.



3- Aldose-Ketose isomerism (functional group isomerism): Have the same molecular formula but differs in **functional group**.

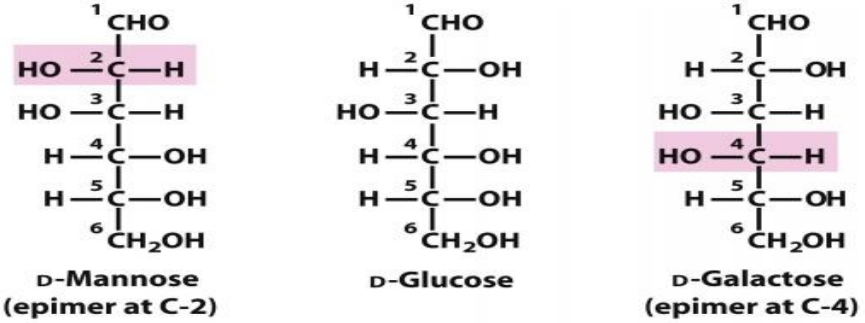
EX: Fructose & glucose One contains **Ketone** group (C=O) and the other contains **aldehyde** group (-CHO). Both are isomers.

4- Epimers: كربونه واحده بس هي اللي مختلفة

A. **Epimers are** isomers having **more** than asymmetric carbon, **all are same** except **only one** is different.

a. **Glucose & Mannose are epimers at** carbons 2.

b. **Glucose & Galactose are epimers at** carbons 4.



MCQs

1. Which of the following is a ketose?

A) Galactose B) Fructose C) Fucose
D) Mannose E) Xylose

2. Glucose is:

A) Source of energy B) Not reducing sugar C) Ketohexose
D) Not optically active E) Pentosugar.

3. The (D & L) configuration of a sugar is based on its analogy to:

A) D-Glucose B) α D-glucose C) D-Fructose
D) D-Ribose E) D-Glyceraldehyde

4. For a compound to be optically active it must be:

A) Colored B) A protein C) Symmetric
D) Asymmetric E) Plant in nature

5. If you dissolve pure crystals of glucose in water and leave the solution for equilibrium, the solution will contain:

A) α-Glucose only B) β-Glucose only
C) Open chain glucose only E) A mixture of a, β and open chain glucose

6. Glucose and galactose are epimers. This means that:

A) They are mirror images of each other.
B) One is pyranose and the other is furanose.
C) They rotate plane polarized light in opposite directions.
D) They differ only in the configuration about carbon atom number 2.
E) They differ only in the configuration about carbon atom number 4.

7. The reference sugar is:

A) Glucose B) Fructose C) Mannose
D) Ribulose E) Glyceraldehyde

8. Rotation of the plane of polarized light is caused by solutions of all of the following monosaccharides, <u>Except:</u>

(a) Glucose (b) Glyceraldehyde (c) Fructose
(d) Dihydroxyacetone (e) None of the above

9. Ribulose is an example of:

(a) Aldopentose (b) Ketohexose (c) Ketopentose
(d) Deoxy sugar (e) Sugar alcohol

10. A pair of Sugars differing from each other in configuration around the functional group is called:

a- Anomers. b- Epimers. c- Racemers. d- Stereoisomers.

11. D-glucose and D-fructose

a- Epimers at C2 b- Epimers at C4 c- Anomers d. Aldose-ketose isomers.

12. Which of the following are Aldohexoses?

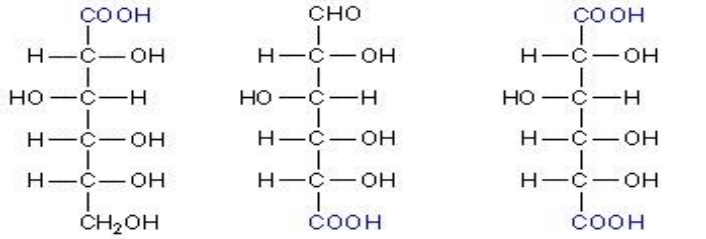
a- Ribose, fructose and erythrose. b- Fructose, ribose, and ribulose.
c- Lactose, sucrose, and maltose. d- Glucose, mannose, and galactose.

Sugar derivatives

1- Sugar acids:

- Are produced by oxidation of **carbonyl carbon**, **last** carbon or **both**.

Carbonyl carbon	**Aldonic acid**	e.g. glucose	gluconic acid.
Last hydroxyl carbon	**uronic acid**	Glucose	glucuronic acid
BOTH	**Aldaric acids**	Glucose	glucaric (saccharic) acid



D-gluconic acid D-glucouronic acid D-glucaric acid

- **L-Ascorbic acid** (vitamin C) is an important sugar acid.

2- Sugar alcohols:

- Are produced by Reduction of **carbonyl carbon**

sugar	Sugar alcohols	function
Glucose	sorbitol	
Mannose	Mannitol	
galactose	Dulcitol	
Glyceraldehyde dihydroxyacetone	glycerol	Structure of Triacylglecerol (TAG) & phospholipid
Ribose	ribitol	Structure of riboflavin (vitamin B_2)
Inositol	Myoinositol **Cyclic alcohol**	Structure of phospholipid It acts as precursor of 2nd messenger
Fructose	mannitol and sorbitol	

3- Deoxysugars:

1. Are produced by replacement of hydroxyl groups by hydrogen atom **i.e.** one oxygen is missed.
2. Occurring in nucleic acid DNA **Ribose** → **De**-oxy ribose.
3. **L-Fucose** (6-deoxyL-galactose): enters in BL.group AG.

4- Amino sugars:

in these sugars, the hydroxyl group attached to **C2** is replaced by an amino or an acetyl-amino group.

1) Amino sugars enter in **glycoproteins**.

2) Examples:

a) Glucosamine: It enters in heparin and hyaluronic acid.

b) Galactosamine: It enters in chondroitin sulphate.
c) Mannosamine: It enters in neuraminic and sialic acids.

5- Amino sugar acids:

1. Formed by addition of **amino sugars** and **some acids**.
2. Examples:
   1- Neuraminic acid = Mannosamine **+** pyruvic acid. → **9C**
   2- Sialic acid or N-acetylneuraminic acid (NANA) → enters in glycolipid.

6- Glycosidic bond and glycosides:

A. Glycosidic bond: It is the bond **between** a carbohydrate **and** another Compound to form a complex carbohydrate.

1. This bond is between the **hydroxyl group** of anomeric carbon of monosaccharide and another compound which may be:

a) Another monosaccharide to form disaccharide.
b) A glycone i.e. non-carbohydrate to form glycoside.

2. **N and O-glycoside bond:**

B. Examples of gilycosides:

1. **Disaccharides**: discussed later.
2. **Sugar nucleotide** as ATP, GTP and other nucleotides: aglycone here is purines And pyrimidines.
5. **Cardiac glycosides:**
   a) Aglycone here is steroid.
   b) Cardiac glycosides such as digitalis.
   C) used in treatment of cardiac disease.

MCQs

13. All the following are sugar alcohols, EXCEPT:

a- Galactitol b- Mannitol c- Xylulose d- Sorbitol

14. Ribitol is:

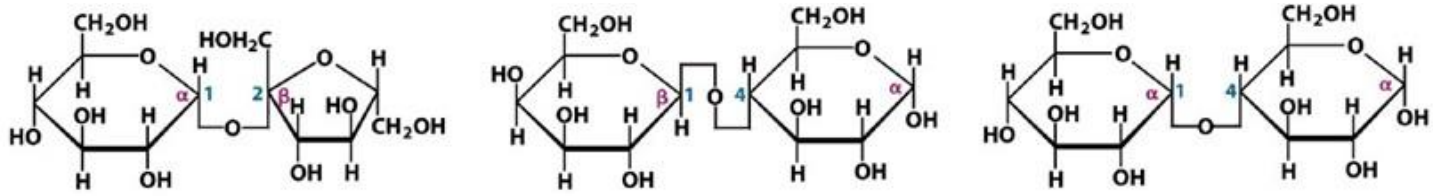
a. Deoxysugar b- Sugar alcohol c- Amino sugar d- Sugar acid

15. Sorbitol is produced by reduction of:

a- Glucose or fructose b- Glucose or galactose
c- Glucose or mannose d- Galactose or fructose

DISACCHARIDES

- **The most important disaccharides are:**
  - {α-glucose + α-glucose} : → **α (1-1)** glycosidic bond → **trehalose**
    → **α (1-4)** glycosidic bond → **Maltose**
    → **α (1-6)** glycosidic bond → **Isomaltose**
  - { α-glucose + β-fructose} : → **(α1-β2)** glycosidic bond **or** (**β**2-1 fructosidic b) → **Sucrose**
  - {β-glucose + β-galactose} : → **β (1-4)** galactosidic bond → **Lactose**
- **Properties:** all disaccharide except (trehalose & Sucrose) showing the following **characters** :
  - It is a **reducing** agent (can reduce Benedict's reagent).
  - It can be present in **α** and **β** forms.
  - It can form characteristic **osazone crystals**.



Sucrose (α-D-Glucopyranosyl-(1 → 2)-β-D-fructofuranose) | Lactose (β-D-Galactopyranosyl-(1 → 4)-α-D-glucopyranose) | Maltose (α-D-Glucopyranosyl-(1 → 4)-α-D-glucopyranose)

Sugar	Source
Maltose	a) Malt. b) **Maltose** is produced during digestion of starch by **amylase** enzyme.
Isomaltose	**Isomaltose** is produced during digestion of starch and glycogen by **amylase** enzyme
Lactose	a) Milk. - **Non-fermentable** sugar.
Sucrose	a) cane and beet sugar (table sugar) b) Pineapple and carrot.

- **invert Sugar** :
  - **Structure:** It is a sugar that contains equal number of both glucose and fructose molecules (unbound).
  - **Sources:** a) Bee honey
    b) By hydrolysis of sucrose by sucrase (invertase) enzyme
  - **Properties:** levorotatory sugar due to strong levorotatory of fructose **invert** the previous dextro-rotatory action of sucrose.

MCQs

16. The sugar found in milk is:

a- Galactose b- Glucose. c- Fructose. d- Lactose.

17. The glycosidic linkage seen in sucrose is:

a- Alpha linkage b- Beta 1-4 linkage
c- Alpha 1-6 linkage d- Alpha 1-2 linkage

18. All the followings have glycosidic bond, EXCEPT:

a- Maltose. b- Sucrose. c- N-acetyl glucosamine. d- Inulin

19. Sucrose consists of:

a- α Glucose + β glucose b- α Glucose + β fructose
c- α Glucose + β galactose d- α Glucose + β mannose

20. Which is a non-reducing sugar?

a- Maltose b- Sucrose c- Lactose d- Isomaltose

21. The glycosidic linkage seen in lactose is:

a- Alpha 1-4 linkage b- Beta 1-4 linkage c- Alpha 1-6 linkage d- Alpha 1-2 linkage

22. The glycosidic linkage seen in maltose is:

a- Alpha 1-4 linkage b- Beta 1-4 linkage
c- Alpha 1-6 linkage d- Alpha 1-2 linkage

23. Hydrolysis of maltose will give rise to:

a. Glucose only b- Glucose and fructose
c- Glucose and galactose d- Glucose and mannose

24. Lactose by hydrolysis gives:

a- 2 glucose molecules b- Glucose and mannose.
c- Fructose and galactose. d- Glucose and galactose.

25. An invert sugar is:

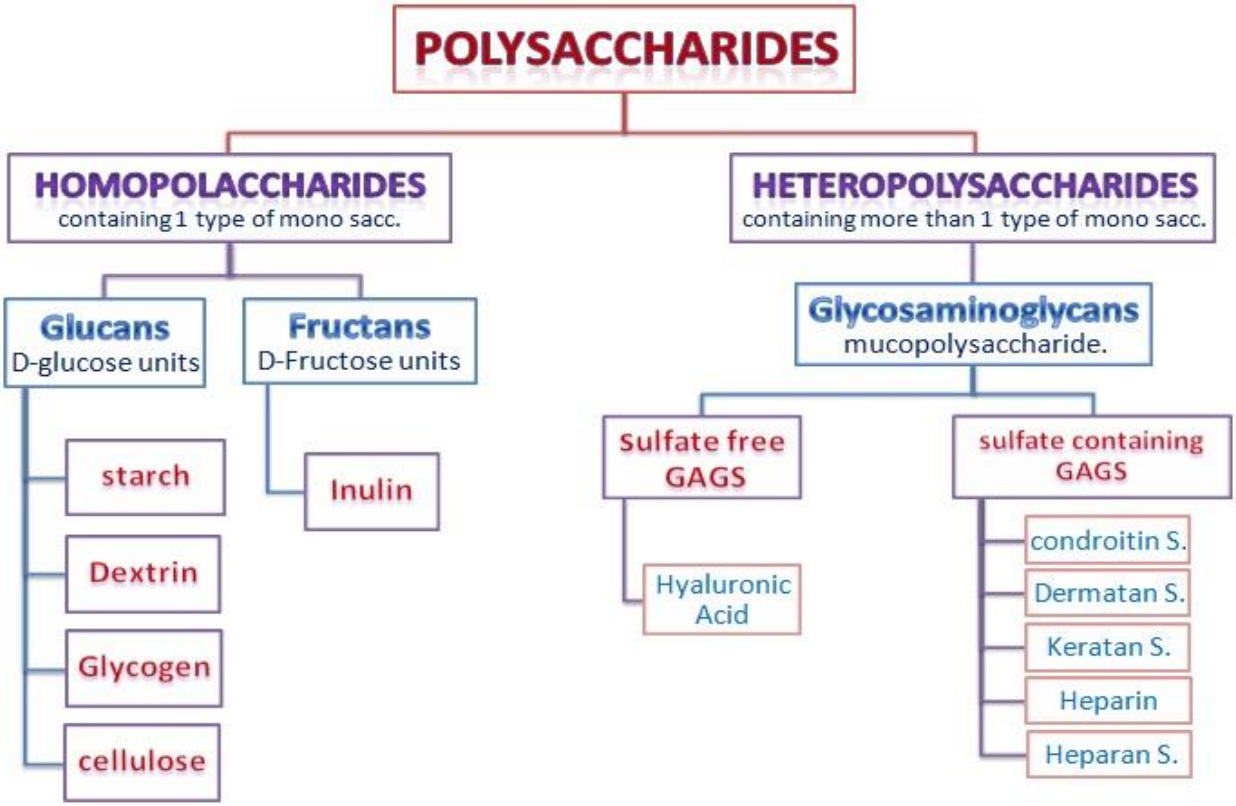
a- An equimolar mixture of glucose and fructose
b- An equimolar mixture of a-glucose and Il-glucose
c- An equimolar mixture of a-fructose and ß-fructose
d- The sugar Which changes its optical activity from levorotatory to dextrorotatory.

26. Osazone formation, mutarotation and reducing property are all based on the presence of:

a- Presence of α form b- Presence of β form
c- Presence of free carbonyl group d- Presence of cyclic structure form

POLYSACCHARIDES

- Thy are polymer of more than 10 unit of monosaccharides or their derivatives e.g. (aminosugar and uronic acid).



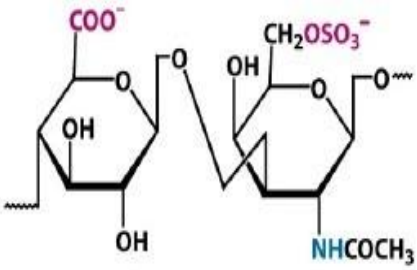
HOMOPOLYSACCHARIDES				
GLUCANS	Starch	Starch granule is formed of: 1) **Inner layer:** called **amylose. It** constitutes 15-20% of the granule and formed of non-branching helical structure of glucose units linked together by α 1 — 4 glycosidic bond. 2) **Outer layer:** called **amylopectin** constitutes 80-85% of the granule and formed of branched chain. Each chain is composed of 24-30 glucose units linked together by α 1 — 4 glycosidic bond and a 1 — 6 glycosidic bond at branching points.	- cereals, potatoes, legumes and other vegetables - In plants it synthesized by photosynthesis.	1) Starch gives blue color with iodine. Amylopectin gives red color with iodine. 2) Partial hydrolysis (digestion) by amylase enzyme gives various forms of dextrins
	Dextrins	- amylodextrin, erythrodextrin and achrodextrin.	- By hydrolysis of starch.	- They give red color with iodine.
	Glycogen	- Highly branched chain - Each branch is composed of 12-14 glucose units. - Similar to amylopectin	- The storage form of CHO in human and animals - in liver, muscles	- gives reddish violet color with iodine
	Cellulose	- long linear chains of (β-D-glucopyranose) linked together by β 1-4 glycosidic bond **- The presence of cellulose in diet is important because it:** - increases the bulk of stool. - This stimulates intestinal movement and prevents constipation.	- plants: vegetables, cotton	- give NO color with iodine - insoluble in water - **Cannot** be digested due to absence of digestive hydrolase enzyme that attacks **β**-linkage.
Fructans	Inulin	- Repeated units of fructose linked together by β1-2 bonds.	- Root of artichokes and other plants.	- Inulin clearance is one of diagnostic tests for investigation of GFR.

Heteropolysaccharides

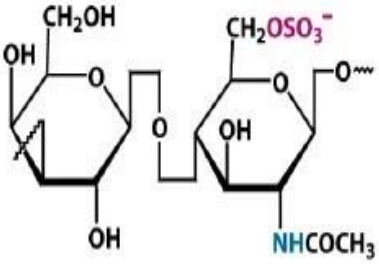
- **Glycosaminoglycans, GAGs (mucopolysaccharide):**

Introduction:

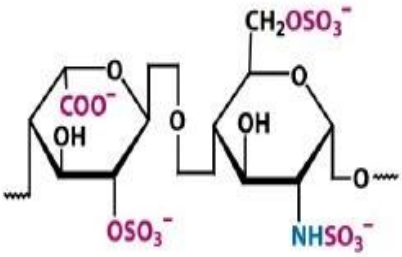
1. They are formed of repeating disaccharide units (Acidic sugar- Amino sugar)$_n$
   a-The acidic sugar is either D-glucuronic acid or its epimer, L-induronic acid.
   b-Amino sugar is either D-glucosamine or D-Galactosamine in which the amino group is usually acetylated. The amino sugar may also be sulfated at carbon 4 or 6.
2. GAGs often contain sulfate group. The uronic acid and sulfate residues cause them to be very negatively charged.
3. They are unbranched and contain no N-acetyl neuraminic acid.
4. Most of GAGs are present extracellularly except heparin.
5. Most of them form the structural components of connective tissue such as bone, elastin and collagen.
6. They act as Lubricants and cushion for other tissues because they have the property of holding large quantities of water.
7. When a solution of glycosaminoglycans is compressed, the water is "squeezed out" and the glycosaminoglycans are forced to occupy a smaller volume, when the compression is released, the glycosaminoglycans return to their original hydrated volume because of the repulsion of their negative charges. This property is the cause of resilience of synovial fluid and the vitreous humor of the eye.



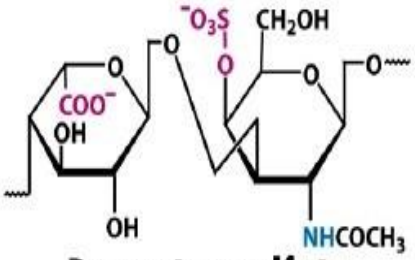
Chondroitin 6-sulfate



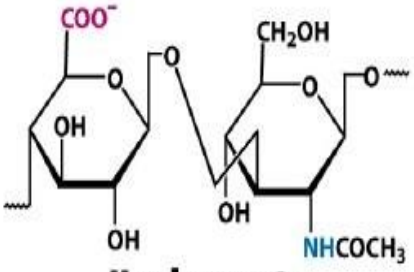
Keratan sulfate



Heparin



Dermatan sulfate



Hyaluronate

Type	Structure	Site	Functions
Hyaluronic acid	Glucuronic acid	Cartilage	lubricant in joints
		Synovial fluid	makes cartilage **compressible**
	N-acetyl glucosamine NO Sulfate	Connective tissue	cell migration during **wound repair**
		Vitreous humor of the eye	cell migration during **morphogenesis**
Chondroitin 4- and 6 sulfate	Glucuronic acid	sage, tendons, ligaments and bones	Have role in compressibility of cartilage in weight bearing
	N-acetylgalactosamine with sulfate on either C4 or C6	Aorta, skin, cornea, umblical cord and in certain neurons	it binds collagen and hold fibers in strong network
Keratan sulfate	Galactose (no uronic acid), with sulfate on C6	Cornea	corneal transparency
	N-acetyl glucosamine with sulfate on C6	Found in Cartilage	
Dramatan sulfate	L-Induronic acid	Cornea	corneal transparency
	N-acetylgalactosamine with sulfate on C6	Sclera. Skin, blood vessels and heart valves	Maintaining the shape of the eye.
Heparin	Induronic acid with sulfate on C2	mast cells (intracellular compound) in the wall of blood vessels	anticoagulant
	Glucosamine with sulfate on C2 and C6		
Heparan sulfate		cell membrane	- act as receptors - cell adhesion and cell-cell interaction
		basement membrane of the kidney	Determining the charge selectiveness of glomerular filtration.

CONJUGATED CARBOHYDRATE

- Glycolipids
- Glycoproteins and proteoglycans
- Fibronectin
- Laminin

	Glycoproteins	proteoglycans
Definition	Are proteins that contain oligosaccharide chains.	chains of glycosaminoglycans attached to protein molecule
1- Structure	Oligosaccharide units.	Glycosaminoglycans.
CHO component		
Ptn component	Protein core	Protein
Types of sugar	Contain no uronic acid	Contain uronic acid
	Pentoses: as arabinose and xylose.	Sugaramines as glucosamines.
	Methylpentoses: L-fucose	
Sulfate group	Contain no sulfate	Contain sulfate.
Size of CHO component	2-15 units.	More than 50 units.
Repeating structure	Little or non.	Repeating disaccharides.
Shape	Usually branched	Linear, unbranched.
2- Function	- Extracellular matrix. - Mucin. - Blood group antigens e.g. A, B and AB. - Cell receptors. - Glycophorins. - Plasma proteins. - Some hormones. - Enzymes. - Antibodies.	- ground substance and support tissues as cartilage, bone and tendons - cell membrane

MCQs

27. The heteropolysaccharide which does not Contain sulphuric acid is:

a- Keratan sulphate b- Dermatan sulphate
c- Chondroitin sulphate d Hyaluronic acid

28. All the following are glucosans EXCEPT:

a- Starch b- inulin c- Cellulose d- Glycogen

29. Amylopectin is characterized by all of the following, EXCEPT:

a- It is a branched polymer.
b- It is structure is very near to glycogen.
c- Contains a IA and a glucosidic bond.
d- Hydrolysis by amylase gives maltose and fructose.

30. Cellulose is characterized by all of the following, EXCEPT:

a- it is a glucosans
b- Linear polymer
c- Consists of β-glucose units
d- Easily digested as it contains β glucosidic bonds

31. Cellulose is not digested as:

a- It contains α-glucosidic bond. b- It contains β -galactosidic bond.
c- It contains β -glucosidic bond. d- It contains α-fructosidic bond.

32. Heparin is:

a- A disaccharide b- An oligosaccharide c- An amino sugar
d- A non-sulfated mucopolysaccharide e- A sulfated mucopolysaccharide

33. Hyaluronic acid ¡s:

a- Glycoprotein
b- Sulfated glucuronic acid
c- Repeated disaccharide formed of glucuronic acid and N-acetyl glucosamine
d- High molecular weight positively charged Homopolysaccharide

CHAPTER 2

Lipids Chemistry

Lipids Chemistry

❖ **Introduction to lipids:**

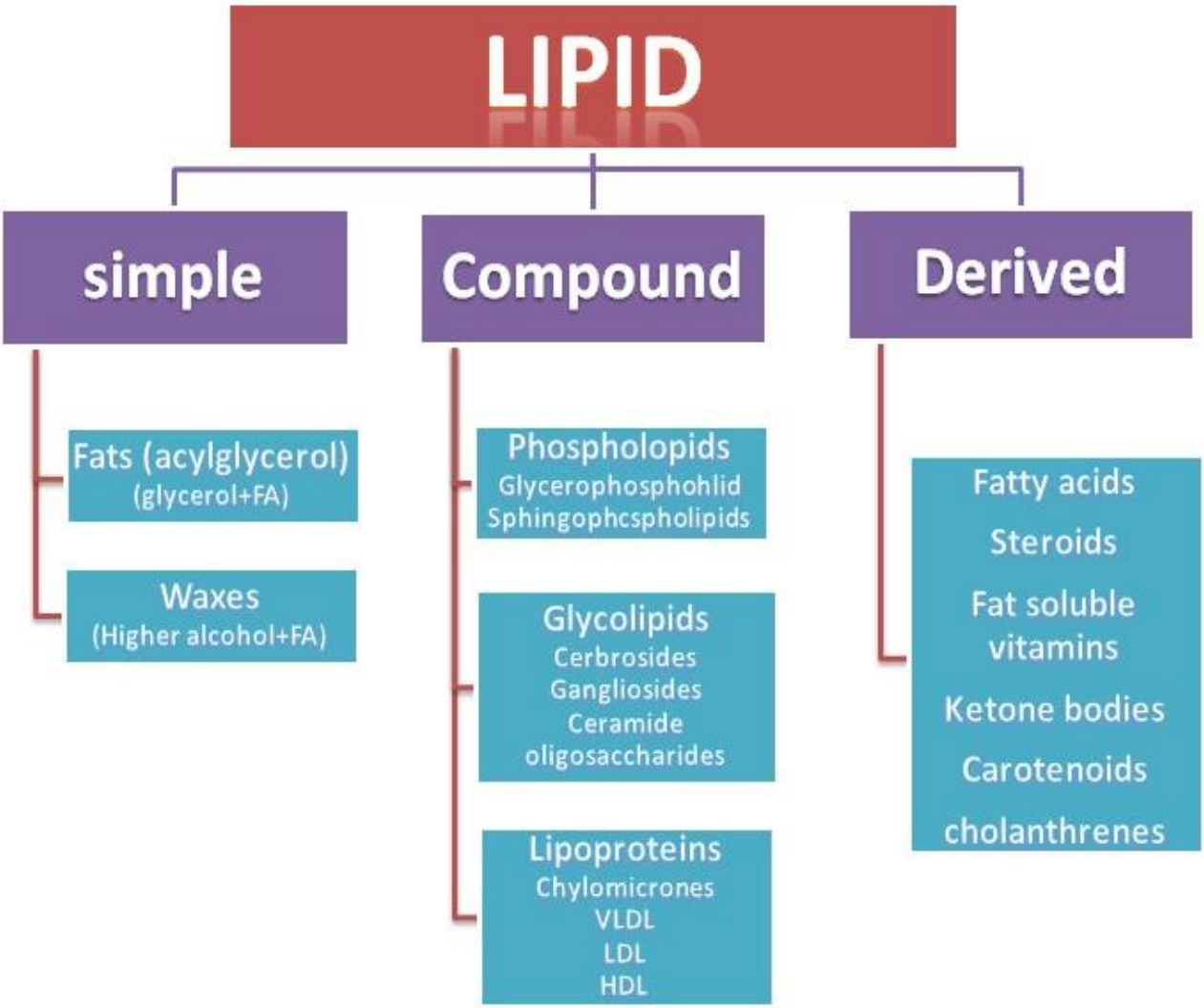
a. **Definition:** Lipids Organic compounds related to fatty acids **insoluble** in water but **soluble** in organic solvents i.e. ether, benzene, acetone & chloroform.

b. The **hydrophobic** nature of lipids is due to the predominance of **hydrocarbon** chains **(-CH_2-CH_2-CH_2-)** in their structure.

❖ **Biomedical Importance:**

1. **Source of energy:** (Lipids have a high energy value)
2. **Supply body e'**:
   - Fat soluble vitamins (vit. K, E, D & A).
   - Essential Fatty acid (a Linolenic & Linoleic acids).

❖ **Classification:**



Simple lipids

❖ **Definition:** Are **esters** of fatty acids with various alcohols. (Ester bond = -COO-). They are either **fats** or **waxes**.

Fatty acids: R.COOH

- Fatty acids are **water-insoluble** "long chain hydrocarbons".
- They are mostly monocarboxylic i.e. having one carboxyl group at the end of the chain (-COOH).
- They are mostly **aliphatic** (i.e. not branched). A few **branched** chain fatty acids are present in **animals** and **plants.**
- Fatty acids may be **Saturated:** (no double bonds) or
  Unsaturated: (containing one or more double bonds).
- Fatty acids may be **Essential:** can**not** be synthesized in the body or
  Nonessential: can be synthesized in the body.
- Fatty acids occur mainly as **esters** in natural fats and oils.
- Fatty acids may also present as free fatty acids **(FFA)** in the plasma carried on **PP**.
- **Short chain F.A :** less than 10 C , **long chain F.A:** more than 10 C

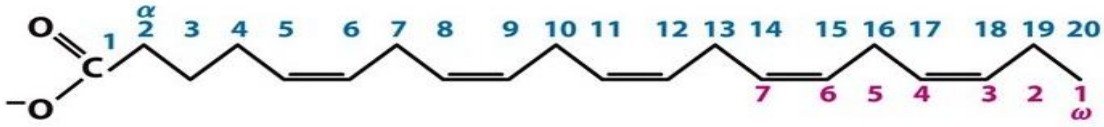
❖ **Numbering of carbon atoms:**

1. Starting from the carboxyl group:

- **1, 2, 3 system:** Give **COOH** No. 1 then proceed to the terminal CH_3.
- **α, β, system:** the 1st carbon following COOH is α then proceed to the terminal CH_3.

2. Starting from the terminal methyl group (omega "ω" carbon):

- The terminal methyl carbon is given ω_1 then proceeds to COOH group



20:5($\Delta^{5,8,11,14,17}$) Eicosapentaenoic acid (EPA)

❖ **Position of double bonds:** The most commonly used systems for designating the Position of double bonds in unsaturated fatty acids are:

(1) The delta (Δ) numbering system e.g. palmitoleic acid **C 16:1 Δ^9** means that this acid contains 16 carbons (16) and one double bond (1) and the position of double bond is between carbon number **9** and carbon number **10** starting from **carboxyl carbon 1**

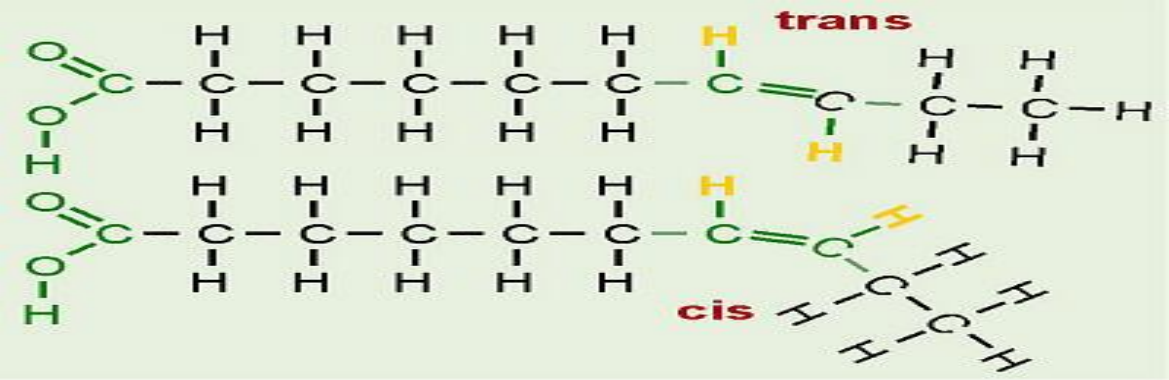
(2) Omega (ω) system e.g. the palmitoleic acid may be written as: **C 16:1 ω^7** which indicates a double bond on seventh carbon counting from the **ω**-carbon atom i.e. last **$-CH_3$** carbon.

- Cis and Trans double bonds: Double bonds in naturally occurring fatty acids in mammals are always in a **Cis** form (configuration) not as Trans form: polyunsaturated acids:

a) Cis form that the groups are on the **same** side.

b) Trans form means that the groups are on the **opposite** sides.

- Trans fatty acid may be present in certain foods, during hydrogenation of oils to manufacture margarine.



❖ **Aliphatic & Branched chain fatty acids:**

Almost all fatty acids present in mammalian tissues are **aliphatic** i.e. straight chain. However, branched- chain fatty acids are found in nature.

A. **Phytanic acid (18C)**:

- Some **milk** products contain branched chain fatty acids called **Phytanic acid** it contains 4 methyl groups at position 3, 7, 11 and 15 carbons.

B. Refsum's disease:

1. It is caused by inability of **oxidation** of Phytanic acid this leads to its accumulation in plasma and tissues.
2. Manifestations: nervous tissue damage in the form of **blindness** and **deafness.**

❖ **Saturated & Unsaturated fatty acids**

i. Saturated fatty acids

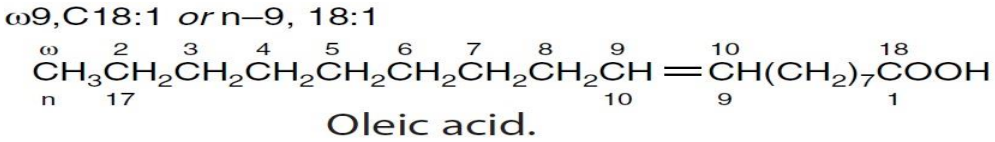
- Have no double bonds in the chain.
- Their general formula is **$CH3- (CH_2)_n -COOH$** where (n) equals the number of methylene (-CH2) groups between the methyl and carboxylic groups.
- The systemic name of saturated fatty acids ends by the suffix (-anoic) e.g. palmitic acid (16c) has systemic name hexadecanoic acid (Hexa =6, Deca =10).
- **Example of the formula of some saturated fatty acids:**
  - **Butyric acid (4c)** = $CH_3- CH_2- CH_2- COOH$
  - **Palmitic acid (16c)** = $CH_3 - (CH2)_{14} - COOH$
  - **Stearic acid (18c)** = $CH_3 - (CH2)_{16} – COOH$

Name	N.O of C	occurrence
Formic	1	Takes part in the metabolism of "C_1" units (formate)
Acetic	2	Major end product of carbohydrate fermentation by rumen organisms.
Propionic	3	
Butyric	4	In certain fats in small amounts (especially butter).
Palmitic acid	16	Common in all animal and plant fats
Stearic acid	18	
Arachidic	20	Peanut (arachis) oil

ii. Unsaturated fatty acids:

- The general formula is **(C_n- H_{2n-1}- COOH).**
- The systemic name of unsaturated fatty acids ends by the suffix **(-enoic)** e.g. **oleic acid** (18c) has systemic name octadecenoic acids.
- Unsaturated fatty acids are either **monounsaturated** or **polyunsaturated**.

❖ **Monounsaturated fatty acids** (**monoethenoic, monoenoic**) i.e. contain **one** double bond e.g. **palmitoleic** acid (16:1 Δ^9) and **oleic** acid (18:1 Δ^9).



❖ **Polyunsaturated fatty acids** **(essential fatty acids=polyethenoic =polyenoic fatty acids =PUFA)** Containing **more than one** double bond: e.g

- In polyunsaturated F.A. each 2 double bonds are separated by methylene group **(-CH_2)**
- **PUFA** are classified according to the position of the 1st double bond in relation to **ω** carbon into ω_3, ω_6, ω_7 & ω_9 F.A.

▪ **ω_3 PUFA:**

i. PUFA having the 1st double bond at carbon **3** in relation to ω carbon

ii. E.X:

1. α Linolenic acid (18:3) —> Parent FA
2. Timnodonic acid (20 : 5)
3. Cervonic acid (22 : 6)
   - α Linolenic is the precursor of other members of this group in the body.

▪ **ω_6 PUFA:**

1. Linoleic acid (18:2) —> Parent FA
2. γ Linolenic acid (18:3)
3. Arachidonic acid (20:4)

a) **Linoleic** (**18:2** $\Delta^{9'12}$, ω^6) and lenolenic (**18:3** $\Delta^{9'12'15}$, ω^3):
   1. They are present in linseed oil.

b) **Arachidonic acid** (**20:4** $\Delta^{5'8'11'14}$, ω^6).
   1. It is present in peanut oil
   2. It is a component of phospholipids in animal.
   3. It is a precursor of a group of compounds called: **eicosanoids**.

Number of C Atoms and Number and Position of Double Bonds	Family	Common Name	Systematic Name	Occurrence
Monoenoic acids (one double bond)				
16:1;9	ω7	Palmitoleic	*cis*-9-Hexadecenoic	In nearly all fats.
18:1;9	ω9	Oleic	*cis*-9-Octadecenoic	Possibly the most common fatty acid in natural fats.
18:1;9	ω9	Elaidic	*trans*-9-Octadecenoic	Hydrogenated and ruminant fats.
Dienoic acids (two double bonds)				
18:2;9,12	ω6	Linoleic	all-*cis*-9,12-Octadecadienoic	Corn, peanut, cottonseed, soybean, and many plant oils.
Trienoic acids (three double bonds)				
18:3;6,9,12	ω6	γ-Linolenic	all-*cis*-6,9,12-Octadecatrienoic	Some plants, eg, oil of evening primrose, borage oil; minor fatty acid in animals.
18:3;9,12,15	ω3	α-Linolenic	all-*cis*-9,12,15-Octadecatrienoic	Frequently found with linoleic acid but particularly in linseed oil.
Tetraenoic acids (four double bonds)				
20:4;5,8,11,14	ω6	Arachidonic	all-*cis*-5,8,11,14-Eicosatetraenoic	Found in animal fats and in peanut oil; important component of phospholipids in animals.
Pentaenoic acids (five double bonds)				
20:5;5,8,11,14,17	ω3	Timnodonic	all-*cis*-5,8,11,14,17-Eicosapentaenoic	Important component of fish oils, eg, cod liver, mackerel, menhaden, salmon oils.
Hexaenoic acids (six double bonds)				
22:6;4,7,10,13,16,19	ω3	Cervonic	all-*cis*-4,7,10,13,16,19-Docosahexaenoic	Fish oils, phospholipids in brain.

❖ **Essential and nonessential fatty acids:**

A. Nonessential fatty acids:

1. These are fatty acids which **can be synthesized in the body**. Thus they are not necessary to be obtained from the diet.
2. They include all **saturated** and **monounsaturated** fatty acids as **palmitoleic** and **oleic acid**.
3. They can be synthesized from acetyl COA (active acetate) derived from glucose oxidation.

B. Essential fatty acids:

a) These are fatty acids that **cannot be synthesized in the body**. They must be obtained from the diet.

b) They include fatty acids that contain more than one double bond **(polyunsaturated fatty acids)** e.g. **lenoleic, lenolenic, arachidonic** acids.

c) The human body has enzyme system that can form only **one double bond** at the **ninth** carbon atom.

Sources:

a) Vegetable oils e.g. corn oil, soya bean oil, safflower oils, sunflower, linseed oil and cotton seed oil.

b) Fish oils: shark liver oils, which particularly contain the ω^3 polyunsaturated fatty acids.

Importance:

a) Normal growth.

b) They enter in the structure of phospholipids and cholesterol esters.

c) They enter in the structure of **cell membranes** and are required for the fluidity of membrane structure.

d) They protect against **atherosclerosis** and **coronary heart disease** by **decreasing** free cholesterol and LDL.

❖ Eicosanoids

A. **Definition:** These are **cyclic** compounds that derived from **arachidonic** acid (eicosatetraenoic)(20 C) after cyclization of its carbons chain to form a ring.
- Hormone like molecules produced by most mammalian cells
- Active within the cell in w' they are produced (autocrine) or on adjacent cells (paracrine)
- Have many physiological & pathological & Pharmacological actions

B. **Components of eicosanoids:**

1. **Prostanoids:** which comprise **prostaglandins**, **prostacyclins** and **thromboxanes.**
   a) **Prostaglandins (PG)**
      1) **PGE_2**: vaso**dilata**tion, relaxation of the uterus and intestine.
      2) **PGF_2 :** vaso**constric**tion, **contraction** of the uterus and intestine.
   b) **prostacyclins**
      They cause **vasodilatation** and **inhibit** platelets aggregation
   c) **thromboxanes**
      They **cause** platelets aggregation
2. **Leukotriens (LT):**
   a) They are present in **leucocytes, platelets** and **mast cells.**
   b) They cause **chemotaxis** i.e. Collection of white blood cells at the site of inflammation (↑ vascular permeability).

❖ Properties of fatty acids:

A. **Physical properties:**

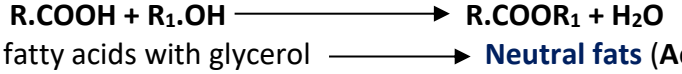
1. **Solubility:**
   a) **Short chain fatty acids** **e.g.** acetic (2C), butyric (4C) and caproic (6C) are **soluble in water**
   b) **Long chain fatty acids** are **insoluble in water** but soluble in nonpolar fat solvents.
2. **Melting point :** It depends on the **length** of the chain of fatty acids and the **degree of unsaturation**, so:
   a) **Short chain** and **unsaturated** fatty acids are **liquid** at room temperature.
   b) **Long chain saturated** fatty acids are **solid** at room temperature.

B. **Chemical properties:**

❖ Properties due to "COOH" group:

1. **Salt formation (soap):** Fatty acids form soap (salts) with **alkalies** as NaOH, KOH, $Ca(OH)_2$:

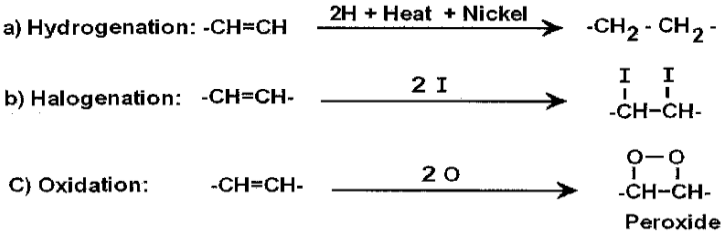
2. **Ester formation:**
   a) Fatty acids form **esters (R.COO.R)** with **alcohols**:



   1) Esters of fatty acids with glycerol → **Neutral fats** (**Acylglycerols**).
   2) Esters of fatty acids with higher alcohols → **waxes**
3. **Reduction:**

❖ Properties due to double bond:

2. **Hydrogenation, halogenation and oxidation:** These are



Alcohols: R.OH

I. Introduction: Alcohols associated with lipids include **glycerol, cholesterol and higher alcohols** (e.g. cetylalcohol, **$C_{16}H_{33}OH$**) usually found in the **wax**.

II. Glycerol: It is polyhydric alcohol containing 3 (-OH) groups:

- **Properties:**
  1. Glycerol is colorless, odorless, and hygroscopic and has sweet taste.
  2. It is soluble in **water and alcohol** insoluble in **nonpolar solvents**
  3. It combines with one fatty acid to form monoacylglycerol, and so on
- **Acrolein:** It is an aldehyde substance with a characteristic odour.
  It derives from glycerol by losing 2 water molecules.
- **Uses of Glycerol:**
  1. **Nitroglycerol** is used as a drug for dilatation of coronary artery.
  2. **Glycerol** enters in manufacturing of creams and lotions for dry skin

III Cholesterol: is an alcohol and derived lipids (see later)

IV. Higher alcohol: long chain contain **one (-OH)** group i.e. monohydric alcohols.

Simple lipids

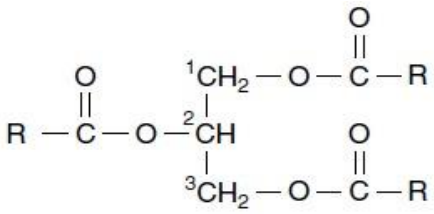
A. They are called simple because they are formed only from **alcohols** and **Fatty acids**. There are two classes of simple lipids (according to the type of alcohol): **acylglycerols** and **waxes**.

- **Acylglycerols** are esters of **one**, **two** or **three** fatty acids with **glycerol**

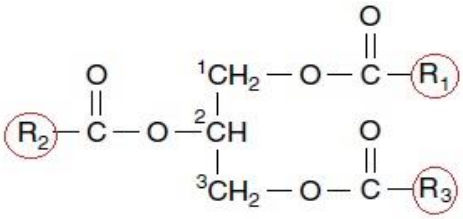
B. Numbering of carbons of glycerol is either: **α, β** and **γ** or **1, 2** and **3**. **Notice that** carbon **1** and **3** of glycerol in Triacylglycerols are not identical when viewed in 3 dimensions. Enzymes can differentiate between the two positions.

i.Triacylglycerols (triglycerides):

- They are called **neutral** fat because they carry **no** charge.
- **Body triacylglycerols:**
  - **Location:** They are stored mainly in cytoplasm of adipose tissue cells (which is located subcutaneously and around kidney and other organs).
  - Body fat is important source of **energy**. Each gram fat gives 9.3
  - Human fat is **liquid** at room temperature and contains high contents of oleic acid.
- **Dietary sources of triacylglycerols:**
  - **In animals** e.g. butter and lards.
  - **In plants** e.g. Cotton seed oil, linseed oil, sesame oil and olive oil.
  - **Marine oils** e.g. cod liver oil and shark liver oil.
- **Types of triacylglycerols:**
  - **Simple triacylglycerols: similar 3** fatty acids are attached to **glycerol**.
  - **Mixed triacylglycerols: 3 different** fatty acids are attached to **glycerol**.



Simple triacylglycerols



Mixed triacylglycerols

❖ **properties of triacylglycerols:**

A. Physical properties:

a. **Solubility: All** triacylglycerols are insoluble in water, soluble in fat solvents.

b. **Melting point:**

- Triacylglycerols rich in unsaturated F.A. are **liquid** at room temperature. **"Oils"**.
- Triacylglycerols rich in saturated F.A. are **solid** at room temperature **"Fats"**.

c. **Specific gravity:** It is **less** than **one**. Specific gravity of water is one Therefore, triacylglycerols float on the surface of water.

d. **Grease stain test:** All Triacylglycerols give **+ve** grease stain test.

B. Chemical properties:

1. **Hardening (Reduction):**

   Def: Hydrogenation of oils to form solid fat or margarine

   As: USFA are converted to SEA

2. **Hydrolysis of TAG:**

   a. **Acid Hydrolysis:**

   Boiling TAG with acids ⟶ Glycerol + 3FAs

   b. **Alkaline Hydrolysis (Saponification):**

   • **Def:** Hydrolysis of TAG using alkalis

   • **Produces:** Glycerol & Soap

   • **Soap:** Alkaline salt of FA

   TAG + 3KOH ⟶ Glycerol + 3RCOOK (K soap)

   c. **Enzymatic Hydrolysis:**

   TAG by lipase enzyme gives glycerol & 3 FAs

3. **Rancidity:**

   Def: Development of toxic compound with bad flavor (odor & taste) of fats or oils duo to oxidation of USFA.

   Types: Hydrolytic & oxidative.

   1. Hydrolytic Rancidity:

   Cause: Due to presence of **(H2O)** OR **Bacteria** (Contain lipase enzyme).

   • Lipase causes release of short chain F.As which are volatile.

   2. Oxidative Rancidity:

   • Oils are more liable to develop this type of rancidity **why?**

   As: they are rich in USFA.

   • Oxidation at USFA → Peroxides, ketones & aldehydes → Bad flavor

   Q: Addition of vit. E, phenols & quinones may prevent oxidative rancidity why?

   As: They are antioxidants so protects USFA against oxidation.

ii.Waxes

❖ **Def**: Esters of long chain FA **with** long chain alcohols contain **one (-OH)** group.

❖ **Site**: Trunks of trees & fur of animals

❖ **Function:** Acts as a protective coat

❖ **Examples**:

1. **True wax (Bee's wax):** Esters of **palmitic** acid e' **mericyl** alcohol (C30)
2. **Lanolin (in hair):** Esters of cholesterol derivatives
3. **Vit A** (Retinol) esters
4. **Vit D** (Calciferol) esters

❖ **Properties:**

1. They have the same physical properties as fat.
2. They give negative **Acrolein** test because they contain no glycerol.
3. They are not digested by lipase enzyme. Thus they are not utilized.
4. They are solids at room temperature.

	Triacylglycerols	Waxes
Composition	Contain glycerol i.e. give positive **Acrolein** test.	Contain no glycerol so, give negative **Acrolein** test.
Melting point	At room temperature: they are either solids or liquids	At room temperature, they are solids.
Rancidity	They may undergo rancidity.	They do not undergo rancidity.

MCQ

1. The structure of stearic acid is:

a- 16 carbon, no double bond
b- 18 carbon, no double bond
c- 18 carbon, two double bonds
d- 18 carbon, three double bonds

2. The structure of oleic acid can be described as:

a- 16 carbon, one double bond
b- 18 carbon, one double bond
c- 18 carbon, two double bonds
d- 18 carbon, three double bonds

3. The major fat in adipose tissue is:

a- Phospholipid
b- Cholesterol
c- Sphingolipids
d- Triacylglycerol

4. Which of the following is true about linoleic acid?

a- It contains 18 C atoms.
b- It contains 2 double bonds.
c- Not formed inside the body.
d. It is W_3 FA.

5. A saturated F.A which contains 16 C is

a- Palmitoleic acid
b. Oleic acid
c- Stearic acid
d- palmitic acid.

6. All are Correct as regards a-linolenic acid, EXCEPT:

a- It is an essential FA.
b- Dienoic (contains 2 double bounds)
c- It is FA
d-It contains 18 C atoms.

7. True statements about lipids include the following EXCEPT

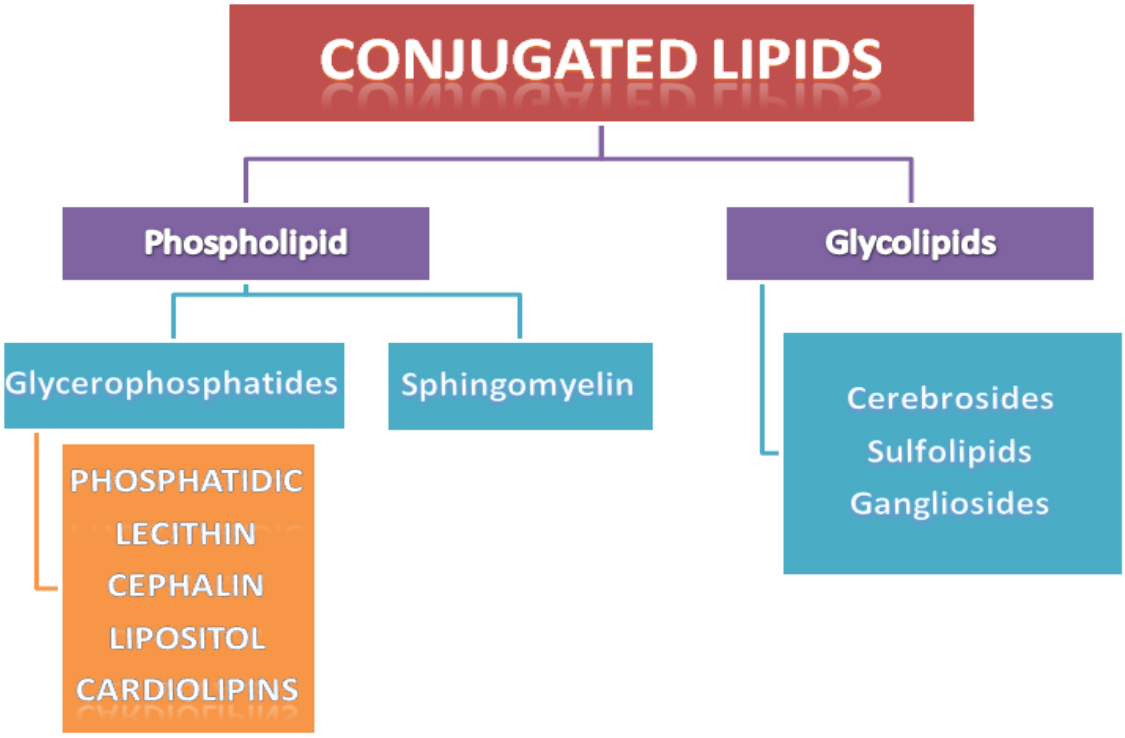
a- They are an intracellular energy source
b-They are poorly soluble in water
c- They are structural components of membranes
d- They are composed Of only carbon, hydrogen and oxygen

8. Fatty acids that are dietary essentials in humans include Which the following:

a- Palmitic acid
b-Stearic acid
c- Oleic acid
d- Linoleic

Conjugated Lipids

- **Def:** Simple lipids conjugated with another group.
- **Classification:**

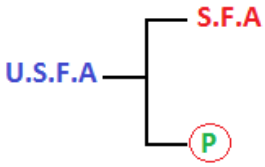


Phospholipids

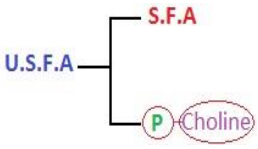
- **Classified according to the alcohol present into**
  - A. Glycerophosphatides (Phosphoglycerides): Containing **(glycerol)**
  - B. Sphingomyelin: Containing sphingosine **(sphingol)**

Glycerophosphatides (Phosphoglycerides)

- Phospholipids containing **glycerol** as alcohol
- They are derivatives of phosphatidic acid.



1. **Phosphatidic acid:**
   - Diacylglycerol phosphate
   - Formed during synthesis of TAG & phospholipid
   - FA at **position 1** is SFA & at **position 2** USFA
   - Other Phosphoglycerides are formed by conjugation of different groups to phosphate



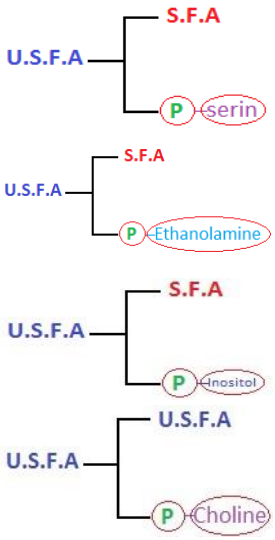
2. **Lecithin (Phosphatidyl Choline):**
   - **Structure:** Formed of phosphatidic acid + Choline
   - **Functions:**
     - Enters in the structure of **cell membrane**.
     - Acts as **lipotropic** factor. I.e. prevent fatty liver.
     - Forms cholesterol ester, Cholesterol esters are transported to the liver, and excreted with bile, This prevent **atherosclerosis**.

$$\text{Lecithin + Cholesterol} \xrightarrow{\text{LCAT}} \text{Cholesterol ester + lysolecithin}$$

     - Lecithin acts as body store of **Choline**. Choline is important for:
       - i- Nerve transmission.
       - ii- Transmethylation: It acts as methyl donor

- **Dipalmityl lecithin** (i.e. lecithin which contains 2 palmitic acid residues)
  Act as a **surfactant in lung**
  i- Dipalmityl lecithin is continuously secreted by the lung cells in the alveolar wall, forming a monolayer over the watery surface of the alveolus and so lowers the surface tension this helps expiration and inspiration
  - **During expiration**, the surfactant becomes **solid** under pressure. This prevents the adherence of alveolar wall.
  - **During inspiration,** The surfactant makes the lung easier to expand.

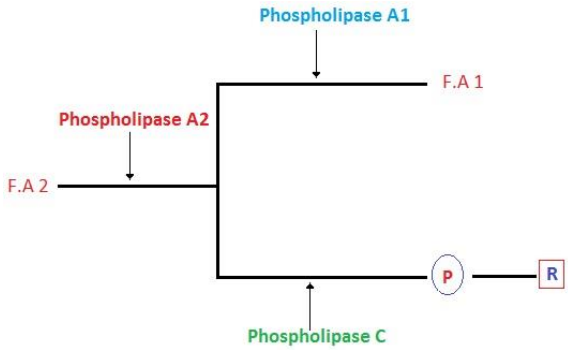
❖ **Respiratory distress syndrome** (hyaline membrane disease):
- In premature babies, lungs do not secrete enough surfactant. This leads to lung collapse and death from respiratory failure.
- **Treatment** of this case needs putting the premature babies in incubator and administration of surfactant locally in the lung.



3. **Phosphatidyl serine:**
   - Formed of phosphatidic acid + serine
4. **Cephalin (Phosphatidyl ethanolamine):**
   - **Structure:** Formed of phosphatidic acid + ethanolamine
   - **Functions:** coagulation mechanism activating factors
5. **Phosphatidyl Inositol (Lipositol):**
   - **Structure:** Formed of phosphatidic acid + Inositol
   - **Functions:** acts as precursor of 2nd messenger "IP_3"
6. **Plasmalogens:**
   - **Structure:** Same structure as lecithin but FA at position 1 is replaced by unsaturated fatty alcohol
   - **Functions:** present in brain & muscles "Lipophilic antioxidants".
7. **Cardiolipins (Diphosphatidyl glycerol):**
   - **Structure:** Formed of 2 molecules of phosphatidic acid connected by 1 molecule of glycerol
   - **Hydrolytic products:** 4FA + 3 Glycerol + 2 Phosphate
   - **Functions:**
   1. Cardiolipins is the major lipid in mitochondrial membrane.
   2. It stimulates antibody formation i.e. antigenic
8. **Lysophospholipids:**
   - **Structure:** Like lecithin and Cephalin, but contains only **1** fatty acid in position**1**
   - **Functions:**
   1. **Lysolecithin** is important in metabolism.
   2. **Lysocephalin** is strong surface-active substance. It is used in manufacturing most types of chocolates.

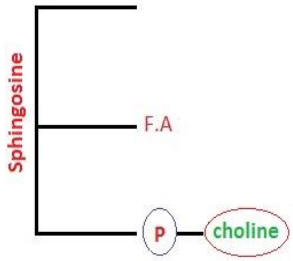
Hydrolysis of Glycerophosphatides

By Phospholipases: Hydrolyzes different phospholipids



Sphingomyelin

- **Structure:**
  1. Sphingosine.
  2. Fatty acid attached to amino group at position 2.
  3. Phosphate at position3.
  4. Choline base (attached to phosphate).



- **Functions:**
  - It is present in high concentrations in brain and nerve tissue
- **Niemann Pick's disease:**
  1. It is accumulation of large amounts of Sphingomyelin in liver due to deficiency of **sphingomyelinase** enzyme.
  2. It leads to mental retardation and death in early life.

GLYCOLIPIDS

- Formed of ceramide (Sphingosine + FA) attached to carbohydrates.
- Includes cerebrosides, Sulfolipids & Gangliosides.

1. **Cerebrosides:**
   - **Structure:** • Formed of **ceramide** + → Glucose (glucocerebroside). / → Galactose (galactocerebroside).
     • FA contain **24** carbons → Cerebronic OR Nervonic
   - **Functions:**
     1- Cerebrosides are present in many tissues especially in the brain and myelin of nerve fibers.
     2- They act as insulators of nerve impulse.
   - **Gaucher's disease:**
     -Def: Accumulation of cerebrosides (sphingolipids) in phagocytes due to deficiency of "β glucocerebrosidase" enzyme.
     -Manifestations: mental retardation, hepatomegally and bone disorder.
2. **Gangliosides:**
   - **Structure:** Formed of ceramide + complex carbohydrate e.g. (NANA)
   - **Function:**
     1. They act as receptors at cell membrane.
   - **Degradation by:** **hexoaminidase** enzyme.
   - **Tay Sachs disease:**
     - Def: Accumulation of gangliosides in brain and intestine due to deficiency of **hexoaminidase** enzyme
     -Manifestations: mental retardation, hepatomegally and blindness.
3. **Sulfolipids (sulfatides):**
   - Formed of ceramide + galactose 3 sulfate.

❖ **Importance of glycolipids : Found in**

- Cell membranes
- Myelin sheath
- Receptors for hormones.

Q1- Enumerate sphingolipids:

- Sphingomyelin
- Glycolipids: (cerebrosides, Sulfolipids, Gangliosides)

Q2: Enumerate Choline containing lipids:

- Lecithin
- Plasmalogens
- Sphingomyelin

Lipoproteins

- These are complex lipids formed of lipids conjugated with protein.
- They are present in c.m, mitochondria and plasma (plasma lipoproteins).
- Plasma lipoproteins convert water **insoluble** lipids into water **soluble** complexes. This facilitates transport of lipids between blood and different tissues.
- The plasma lipids are triacylglycerols, phospholipids, cholesterol (free and esterified) and free fatty acids.
- Methods used for separation of plasma lipids:
  These methods include: electrophoresis, Ultracentrifugation, gas liquid chromatography and thin layer chromatography
- The protein fractions are called **Apo lipoproteins**. **They include :**

FRACTION	SOURCE	MAIN LIPID	ptn Amount	Types
chylomicrons	Intestine	TG	2%	A, B_{48},C & E.
VLDL	Liver	TG	12%	B_{100}, C & E
LDL	Blood from chylomicrons and VLDL	Cholesterol, esters and phospholipids	22%	B_{100}
HDL	Liver	Cholesterol, esters and phospholipids	50%	A, C, D & E.
FFA.Albumin	Adipose tissue	FFA	99%	Albumin

MCQ

9. All the following statements are true with regard to phospholipid EXCEPT:

a- They can exist as zwitter ions
b- They have surfactant properties
c- They are components of biomembranes
d- They are resistant to the action of enzymes

10. Which of the following is NOT a phospholipid?

a- Sphingomyelin. b- Cerebrosides. c- Cephalin. d- Lecithin.

11. Sphingomyelin on hydrolysis yields all the following, EXCEPT:

a- Sphingosine b- Glucose c- Phosphate d- Choline

12. Cardiolipin:

a- Contains choline
b- Is diphosphatidyl glycerol
c- Is a part of sphingolipin
d- Is found in endoplasmic reticulum

13. A ganglioside on hydrolysis gives all the following, EXCEPT:

a- Fatty acid
b- Glycerol
c- Sphingosine
d- N-acetyl neuraminic acid

14. Phospholipids containing choline include all of the following EXCEPT:

a- Phosphatidyl choline.
b- Sphingomyelin
c- Lecithin
d- Cardiolipins.

15. Ceramide consists of:

a- Sphingosine and galactose.
b- Sphingosine and FA.
c- Glycerol and galactose.
d- None of the above.

16. All of the following are glycolipids, EXCEPT:

a- Sulfatides.
b-Lecithin.
c- Ganglioside.
d- Cerebrosides.

17. All are sphingolipids, EXCEPT:

a- Sphingomyelin.
b- Sulfatides
c- Cephalin.

18. The sphingolipid "which contains NANA sialic acid is:

a- Sulfulipids.
b-Gangliosides.
c- Cerebrosides.
d-Sphingomyelin.

19. Which of the following is NOT phospholipid?

a- Cerebrosides
b- Cardiolipin
c- Lecithin
d. Sphingomyelin

20. Sphingosine is the backbone of all the following EXCEPT:

a- Lecithin
b- Ganglioside
c- Cerebrosides
d- Sphingomyelin

Derived Lipids

❖ **Def:**

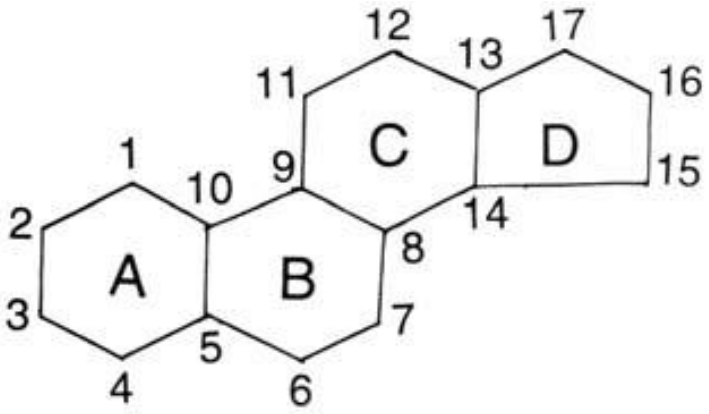
Produced by **hydrolysis** of simple or conjugated lipids or associated with lipids in nature.

❖ **Includes:**

1. FA
2. Steroids
3. Carotenoids
4. Ketone bodies
5. Fat soluble vitamins (Vit. K, E, D & A)

Steroids

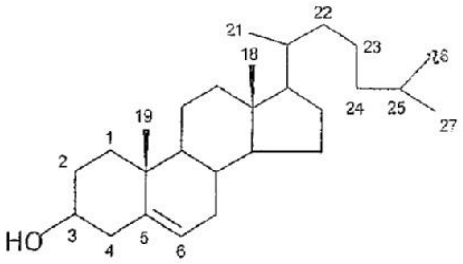
- Compounds containing steroid nucleus **(cyclopentano-perhydro-phenanthrene "CPPP")**



❖ **Types of steroids and sterols are:**

1. Cholesterol (animal origin).
2. Ergosterol (plant origin).
3. Vitamin D group (D_2 and D_3).
4. Bile salts.
5. Steroid hormones:
   a) Male sex hormones.
   b) Female sex hormones.
   C) Adrenocortical hormones.
6. Digitalis glycosides.

Cholesterol



❖ **Structure:**

a. **cyclopentano-perhydro-phenanthrene** ring
b. -OH group at C_3 (so it is an alcohol).
c. 2 methyl groups at C_{10} & C_{13} (- CH_3 = I).
d. Long side chain at C_{17}.

❖ **Body cholesterol:**

a. It is present in everybody cell (cell membrane) especially in:
   - Adrenal cortex.
   - Liver and kidney.
   - Brain and nerve tissue.
b. Blood cholesterol:
   - It occurs in the blood in 2 forms: free form and esterified form (combined to fatty acids to form ester)
   - The level of blood cholesterol is normally less than 220 mg/dl. Any increase above this level is called: **hypercholesterolemia**

❖ **Properties:**

1. It is an alcohol, **in**soluble in water, soluble in fat solvents.
2. It forms characteristic crystals with broken corner.
3. It gives positive Lieberman's test which runs as follows
   cholesterol + Acetic acid + conc. sulphuric acid → **Bluish green color**.

❖ **Functions of cholesterol:** it is important for:

1. **It enters in the structure of everybody cell particularly:**
   a) Cell membranes.
   b) In nervous tissue.
2. **Synthesis of steroid hormones.**
3. **Synthesis of bile salts.**
4. **Synthesis of vitamin D3.**

Ergosterol

❖ **Structure:** Similar to cholesterol but differs in:

a) Extra double bond between C7 & C8.
b) The side chain is unsaturated and has extra methyl group.

❖ **Properties:** It is a plant sterol, poorly absorbed from small

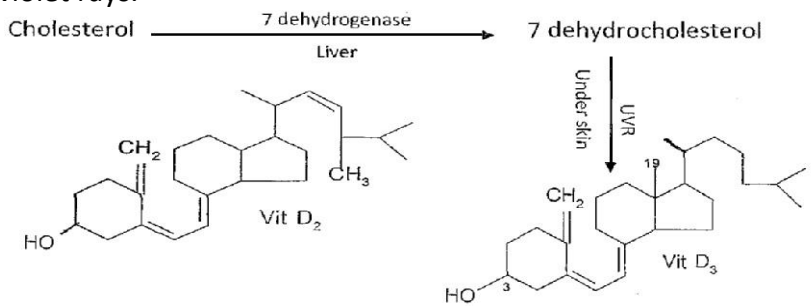
❖ **Functions:** It gives vitamin D_2 by ultraviolet rays.

Vitamin D group

❖ **Structure:**

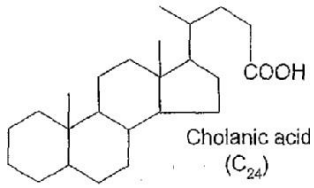
1. Vitamin D_3 is derived from 7-dehydrocholesterol by the rupture of second ring by ultraviolet rays.

2. Vitamin D_2 is derived from ergosterol by the rupture of second ring by ultraviolet rays.



Bile acids and salts

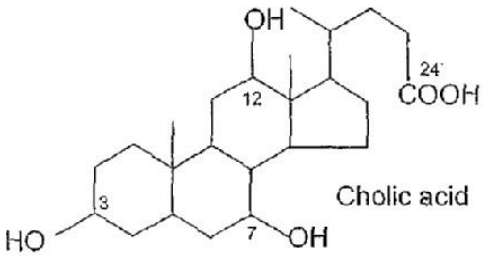
Bile acids are hydroxyl derivatives of C24 steroid termed **cholanic** acid

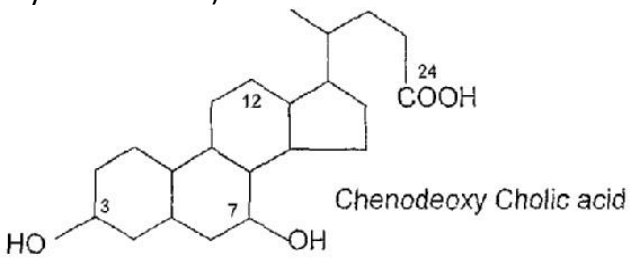


❖ **Types of bile acids:** Primary & Secondary bile acids

A. Primary bile acids

- Cholic acid (3, 7, 12 trihydroxy cholanic acid)
- Chenodexy cholic acid (3, 7 dihydroxycholanic acid)





B. Secondary bile acids

- 2ry bile acids are formed from 1ry bile acids by the action of intestinal bacteria (contain **7α dehydroxylase**).

2ry bile acids are:

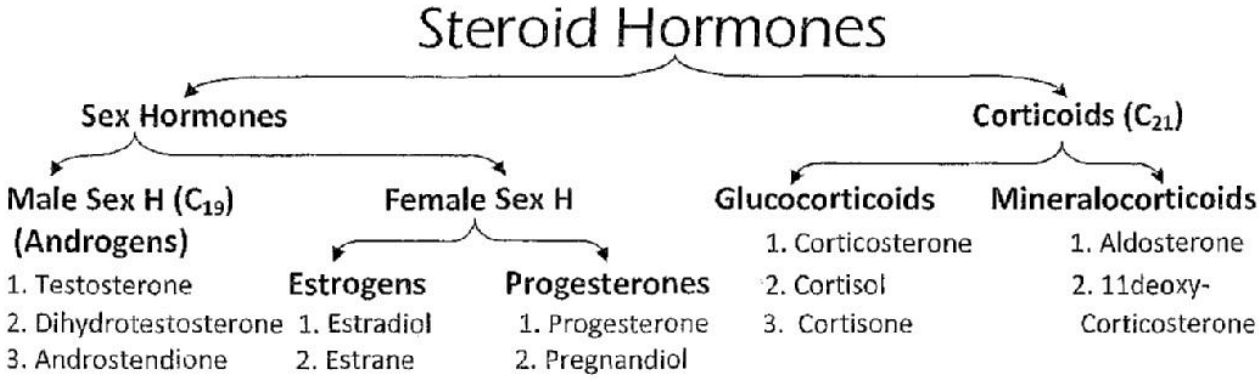
- Deoxycholic acid (3, 12 dihydroxy cholanic acid).
- Lithocholic acid (3 monohydroxy cholanic acid).

C. Bile Salts

- Formed by & conjugation of bile acids with glycine or tourine then Na^+ or K^+ to form: • **Na glycocholate** • **Na taurocholate**
- Bile salts are excreted from **liver** & stored in **gall bladder**
- Bile salts pass to intestine during digestion of fat
- They are reabsorbed from intestine & back to liver (**Enterohepatic circulation**)

❖ **Importance of bile salts: MDAPS**

1. Main way for excretion of cholesterol.
2. Digestion of fat due to emulsification.
3. Absorption of fat due to formation of micelle.
4. Prevents precipitation of cholesterol & formation of cholesterol stones.
S. Stimulates liver cells to secrete more bile (Choleretic effect).



Carotenoids (terpenes)

❖ **Definition:**

a) Carotenoids are among the most common and most important natural Pigments.
b) They have yellow to red color.

❖ **Types and structure:**

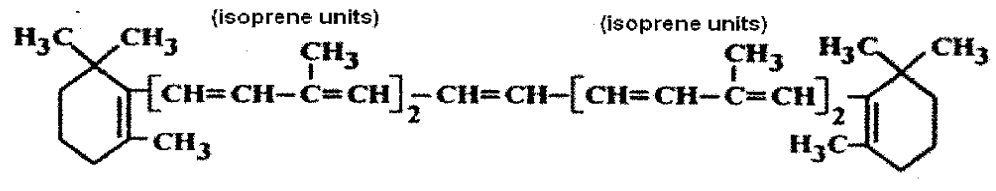
a) Many types are present e.g. α, β and γ carotene.
b) All are hydrocarbons formed only of carbons and hydrogen.
c) Generally each carotene is formed of two ionone rings. Each ionone ring is connected to two isoprene units, both are interconnected by methane group (-CH=CH-).

❖ **Sources:**

a) Plant sources: They are responsible for many colors of fruits and vegetables e.g. carrots, orange, apricot, apple and tomato.
b) Animal sources: fats, butter, milk and egg yolk.

❖ **Functions:**

*** Antioxidant** *** Antimalignant** *** Provitamin A**



β-Carotene

CHAPTER 3

Protien Chemistry

Amino Acids

- **Structure:**

A. There are about 300 amino acids occurring in nature. Only 20 of them occur in proteins.

B. Each amino acid has the following 4 groups or atoms: attached to alpha (α) carbon:

1- Amino group: (NH_2).

2- Carboxyl group: (COOH).

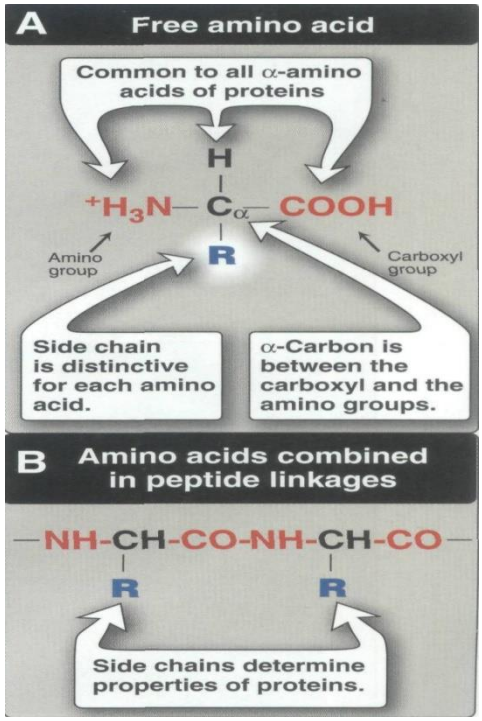
3- Hydrogen atom (H).

4- Side chain or radical group (R).

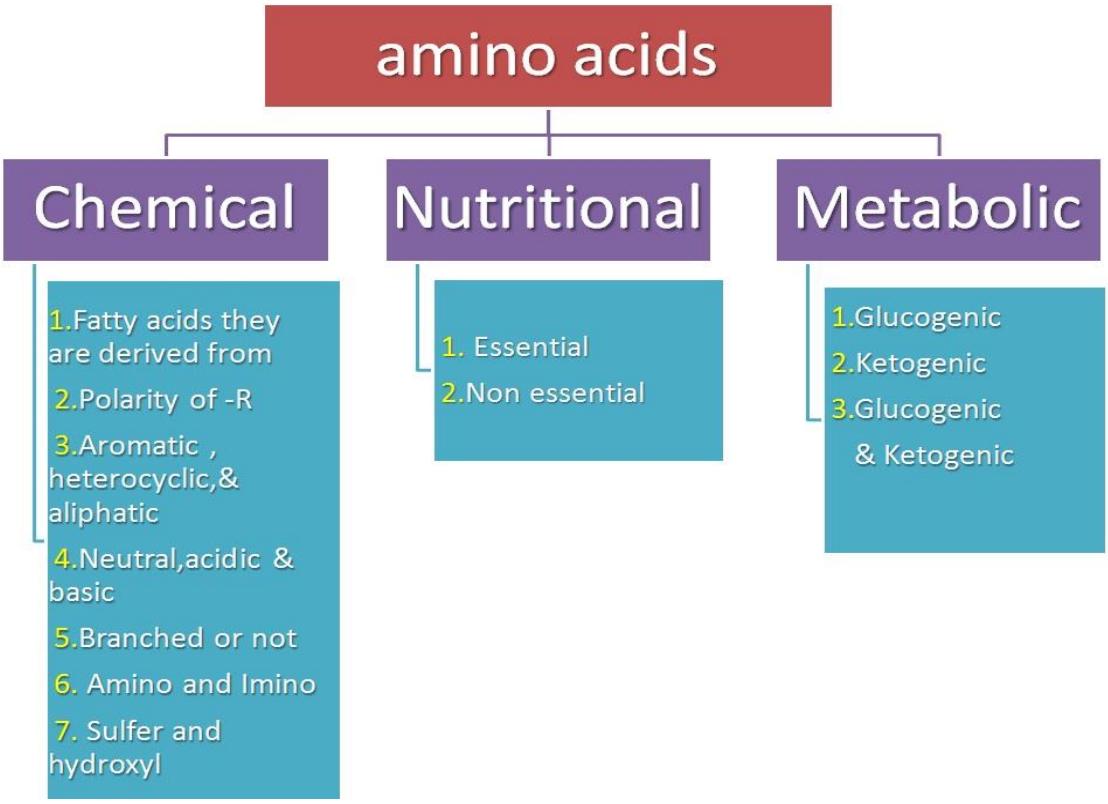
C. Characters of amino acids: all are

1. α-Amino acids: i.e. the amino group attached to the second carbon (next to the carboxyl group).

2. L-Amino acid i.e. α-amino group is on the left side configuration.



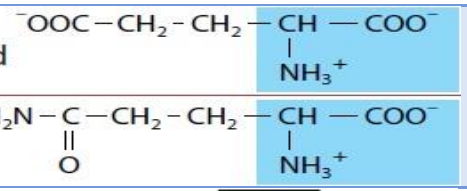
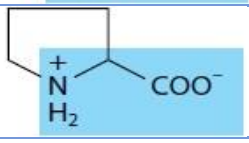
- **Classification of amino acids:**



➢ Chemical classification:

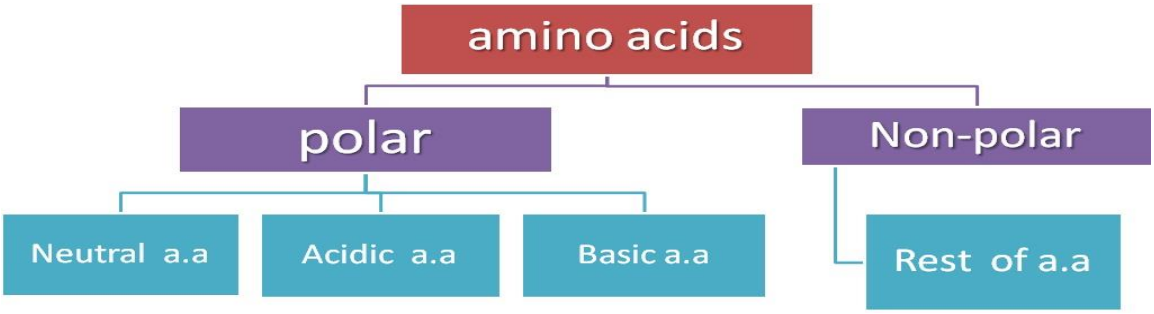
1. According to the fatty acids the amino acids are derived from:

Fatty acids	Amino acids
1- acetic acid: 2c (CH_3-COOH): - Glycine: (alpha amino acetic acid).	Glycine
2- Propionic: 3c (CH_3-CH_2-COOH): - Alanine: (alpha amino Propionic acid) - Serine: (alpha amino beta hydroxy Propionic acid) - cysteine: (alpha amino beta thiol, Propionic acid) - Phenylalanine: (alpha amino, beta Phenyl Propionic acid) - Tyrosine: (alpha amino, beta parahydroxy phenyl Propionic acid) - Tryptophan: (alpha amino beta indole Propionic acid) - Histidine: (alpha amino beta imidazol Propionic acid)	Alanine Serine Cysteine Phenylalanine Tyrosine Tryptophan Histidine
3- butyric acid: 4c (CH_3-CH_2-CH_2-COOH) - Threonine:(alpha amino, beta hydroxy butyric acid) - Methionine:(alpha amino, gamma methyl thiol butyric acid)	Threonine Methionine
4- Valeric acid: 5c (CH_3-CH_2-CH_2-CH_2-COOH) - Isoleucine: (alpha amino, beta methyl Valeric acid) - Arginine: (alpha amino, delta guanido Valeric acid)	Isoleucine Arginine
5- Isovaleric acid: 5c - Valine: (alpha amino, Isovaleric acid)	Valine
6- Caproic acid: 6c - Lysine: (alpha amino, epsilon amino caproic acid)	Lysine
7- Isocaproic acid: 6c - Leucine: (alpha amino isocaproic acid)	Leucine
8- Succinic acid: 4c dicarboxylic acid - Aspartate: (alpha amino succinic acid) - Asparagine:(alpha amino succinic	Aspartic acid Asparagine

9- Glutaric acid: 5c **dicarboxylic acid** - **Glutamate:** (**alpha amino glutaric acid**) - **Glutamine:** (**alpha amino glutaric acid amide**)	Glutamic acid  Glutamine
10- pyrrolidine ring: 4c - **Proline:**	Proline 

2. **According to if the amino acid is acidic, basic or neutral amino acids:**
   a) **Acidic amino acids:** contain more than one -COOH group. e.g. Aspartate and glutamate.
   b) **Basic amino acids:** contain more than one $-NH_2$ group. e.g. ornithine, lysine, Arginine and histidine.
   c) **Neutral amino acids:** these are amino acids, which contain one COOH and one $-NH_2$ groups. e.g. glycine, alanine, etc.

3. **According to the polarity of the radical (R):**

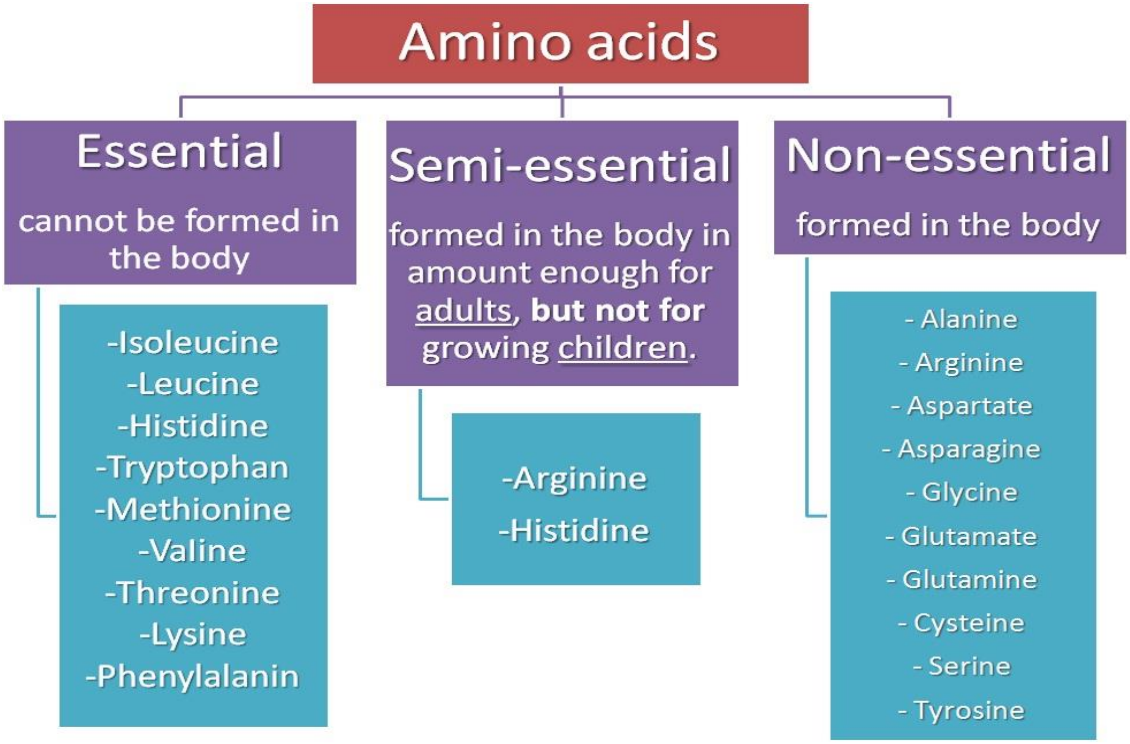


4. **Classification according to if amino acid is: aromatic, heterocyclic or aliphatic.**
   1. Aromatic amino acids: which contain **phenyl** or **phenol** ring:
      a) Phenylalanine (phenyl ring).
      b) Tyrosine (phenol ring).
   2. Heterocyclic amino acids: which contain **other type of rings**:
      a) Tryptophan (indole ring).
      b) Histidine (imidazol ring).
      c) Proline (pyrrolidine ring).
      d) Hydroxyproline (hydroxy pyrrolidine ring).
   3. Aliphatic amino acids: include other amino acids which contain **no ring**.

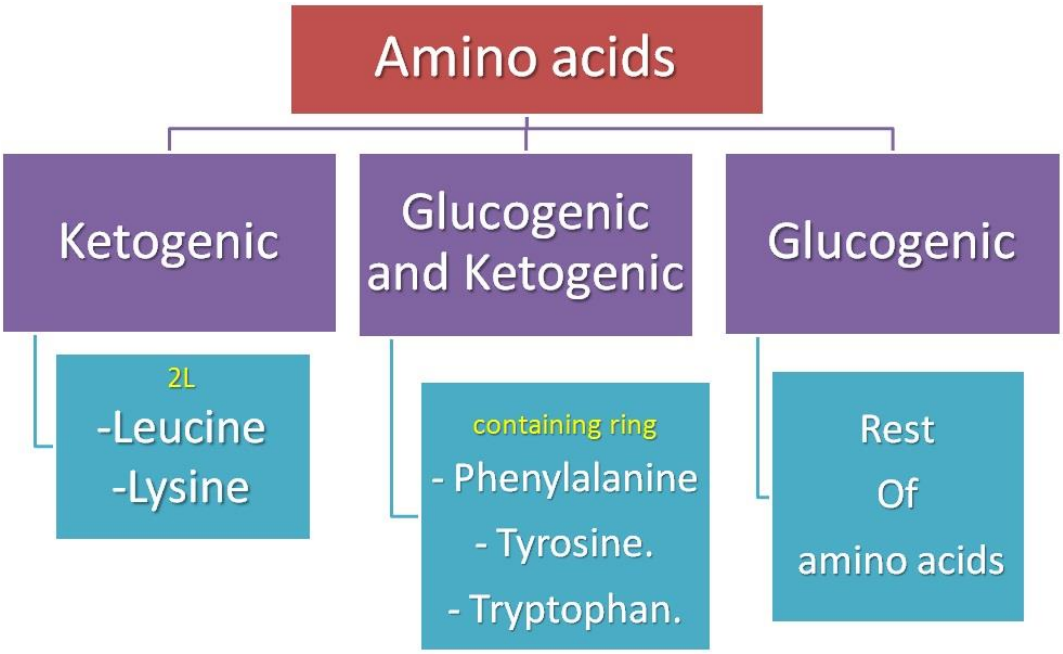
5. **According to if the amino acid is: branched or non branched:**
   1. Branched amino acids: **alanine, Leucine and Isoleucine**.
   2. Non-branched amino acids: **Rest of amino acids**.

6. **Imino and amino acids:**
   1. Imino acids: **Proline and, hydroxyproline.**
   2. Amino acids: **Rest of amino acids.**
7. **Sulfur and hydroxyl containing amino acids:**
   1. Sulfer containing amino acids: **cysteine, cystine and methionine.**
   2. Hydroxyl containing amino acids: **serine, threonine.**

➢ **Nutritional classification of amino acids:**



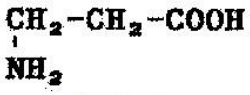
➢ **Metabolic classification:**

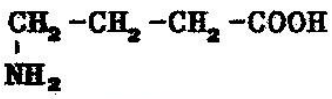


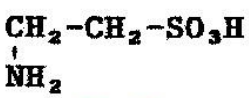
- **Amino acids that do not enter in protein structure:**

A. Non alpha amino acids:

1. **β-Alanine:** It enters in the structure of a vitamin called pantothenic acid
2. **Gamma amino butyric acid (GABA):** This is a neurotransmitter formed from glutamate in brain tissue.
3. **Taurine:** This occurs in bile combined with bile acids.

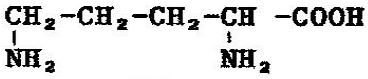

β-Alanine

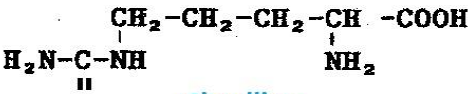

GABA


Taurine

B. Amino acids which participate in urea cycle:

1. **Arginine:** (**α**-amino **δ**-guanido Valeric acid).
2. **Ornithine:** (**α, δ-** diamino Valeric acid).
3. **Citrulline:** (**α**-amino **δ**- urido Valeric acid).


Ornithine


Citrulline

C. Amino acids in intermediary metabolism: -

1. **Homoserine:** (**γ**-Hydroxy **α**-amino butyric acid)
2. **Homocysteine:** (**γ**-Thiol **α**-amino butyric acid)

D. Amino acids containing iodine: These are precursors of thyroid hormones:

1. Monoiodotyrosine.
2. Diiodotyrosine.
3. Triiodotyrosine (T_3).
4. Tetraiodotyrosine (T_4)

E. It is 2 molecules of **cysteine** (dicysteine) united together by removal of hydrogen of -SH groups, It is important for protein structure.

Cystine

- **Function (biomedical importance) of amino acids**

A. Structural function: enter in the structure of:

a) **Body peptides and proteins:** e.g. plasma proteins, tissue proteins, enzymes, etc.

b) **Hormone:** some hormones are amino acid derivatives e.g. thyroxin.

c) **Amines:** Some amino acid gives corresponding amines by decarboxylation e.g. **histidine** gives **histamine** which is vasodilator.

B. Neurotransmitters: Some amino acids as **glycine** and **glutamate** act as N.T

C. Detoxication: Some amino acids are used in detoxication reactions

- **Properties of amino acids:**

Physical	Chemical
A. Solubility: Amino acids may be soluble in water, dilute acids **B. Optical activity:** All amino acids - except glycine are optically active because they contain asymmetric carbon atom. **C. Meltin g point:** Amino acids are present in crystals with high ionic forces, stabilizing these crystals. So amino acids have high melting points above **200°C** i.e. they are very stable molecules. **D. Amphoteric properties and isoelectric point of amino acids** = have both basic ($-NH_2$) and acidic (-COOH) groups. - Monoamino-monocarboxylic acids present in aqueous solutions as **zwitter ion:** It is the amino acid that carries both positive and negative charges. It is electrically neutral and cannot migrate in electric field. - **Isoelectric pH (isoelectric point: Pi): it is the pH at which the zwitter ion is formed.** **1)** Each amino acid has certain pH at Which zwitter ion is formed. **2)** This pH is at midway between the pK values of the carboxyl and amino groups. **3)** Example: **alanine** **i-**In strongly acidic pH (at pH zero) alanine is present mainly in the form of positively charged molecule. Its pK (PK_1) = 2.34 **ii-** By adding **NaOH,** the carboxyl group loses its proton (H^+) and alanine carries both positive and negative charges (zwitter ion). **iii-**By adding more **NaOH,** the solution becomes strongly alkaline, and ($-NH_3$) group will lose its proton and alanine will become negatively charged. Its pK (PK_2) = 9.69. $PI \text{ for alanine} = \frac{pK_1 + pK_2}{2} = \frac{2.34 + 9.69}{2} = 6.105$	**A. Properties of carboxyl** (-COOH) **and amino** (-NH2) **groups:** **B. Reaction with ninhydrin:** **1.** **Ninhydrin** is a substance that reacts with amino acids to give **CO_2, ammonia** and **aldehyde.** **a)** Ninhydrin reacts with liberated ammonia to give **blue** colour. **b)** The intensity of the blue colour indicates the quantity of amino acids present. IT can detect 1 ug of a.a **2.** Ninhydrin reaction is given also by ammonia, peptides and proteins. **3.** Ninhydrin can react with proline and hydroxyproline (**Imino**) but it gives **yellow** **C. Reaction with fluorescamine:** **1.** Like ninhydrin, fluorescamine forms a **blue** complex with amino acids. **2.** It is more sensitive than ninhydrin, and can detect nanogram quantities of a.a **D. Color reactions of amino:** acids These depend on the nature of radical (R). 1-Millon's reaction: for tyrosine→ Red. 2. Rosenheim's R: for tryptophan → Purple. 3. Xanthoproteic R: for phenylalanine and tyrosine → Orange color. **E. Peptide bond formation.** **F. Absorption spectrum of amino acids:** **1.** Amino acids are colorless. They do not absorb visible light. **2.** Aromatic amino acids (particularly tryptophan) absorb ultraviolet light (wave length 250-290 nm).

MCQ

1. One of the amino acids listed below is not basic:

a- Arginine b- Histidine c- Glutamine d- Lysine

2. Which of the following amino acid has a hydroxyl group?

a- Valine b- Threonine c- Leucine d- Histidine

3. All the following amino acids are neutral, EXCEPT:

a- Aspartic acid b- Tyrosine c- Glycine d- Threonine

4. All the following are branched chain amino acids, EXCEPT:

a- Valine b- Leucine c- Isoleucine d- Threonine

5. All the following are Sulphur containing amino acids, EXCEPT:

a- Cysteine b- Methionine c- Homocysteine d- Threonine

6. Guanido group is present in:

a- Arginine b- Tryptophan c- Histidine d- Proline

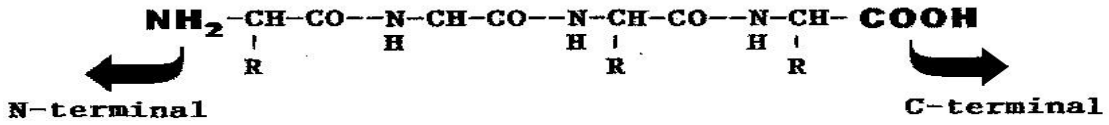
7. Indole ring is present in:

a- Arginine b- Tryptophan c- Histidine d- Proline

Peptides

- **Definition:** Peptides are compounds, formed of less than 50 amino acids linked together by peptide bonds.
  1. Dipeptide (2 amino acids and 1 peptide bond). **3. Oligopeptide** (3-10 amino acids).
  2. Tripeptide (3 amino acids and 2 p.b). **4. Polypeptide** (10-50 amino acids).
- **Peptide bond:**
  - Definition: It is a covalent bond formed between the carboxyl group of one amino acid and the amino group of another.
  - Mechanism: - it is formed by removal of water.
    - Peptide formation needs energy getting from hydrolysis of ATP
  - Characters: - Peptide bond is semi-rigid bond i.e. no free rotation can occur around bond axis.
- **Primary structure of peptides:**

- It's the arrangement of amino acids in a polypeptide chain.
- In a polypeptide chain the N-terminal amino acid (i.e. the only amino acid that contains free amino group) is always to the left side.
- The C-terminal amino acid (i.e. the only amino acid that contains free carboxyl group) is always to the right.



- **Separation of peptides**

A. By electrophoresis **B.** By exchange chromatography technique.

- **Biologically active peptide** Peptides include many active compounds as:

A. Glutathione:

- **Definition:** it is a **Tripeptide** formed of three amino acids: glutamate cysteine and glycine. It is also called "**glutamyl-cysteinyl-glycine**".
  Glutathione is commonly **abbreviated** as **G-SH** where -SH indicates the sulfhydryl group of cysteine and it is the most active part of the molecule.
- **Functions of glutathione:**
  1- Defense mechanism against certain toxic compounds (Detoxification).
  2-Absorption of amino acid: glutathione has a role in transport of amino acids across intestinal cell membrane..
  3- Protect against cell damage and hemolysis of RBCs: Glutathione breakdown the hydrogen peroxide (H_2O_2) which causes cell damage and hemolysis.
  4- Activation of some enzymes.
  5- Inactivation of insulin hormone.

B. Hormones

1. **Insulin** and **glucagon** from Pancreas.
2. **Vasopressin** and **oxytocin** from posterior pituitary gland.
3. **ACTH** from anterior pituitary gland.

C. β-Lipotropin:

- Is polypeptide produced by anterior pituitary.
- Is the precursor of **β-endorphin**.
- **β-endorphin** acts as neurotransmitter and neuromodulator.
- It has **analgesic effect** powerful **18-30** times than morphine.

D. Bradykinin:

1. It is released from specific plasma proteins by specific proteolytic enzyme.
2. It acts as a potent smooth muscle relaxant and produces vasodilatation and hypotension.

E. Antibiotics: e.g. valinomycin.

F. Antitumor agent: e.g. bleomycin.

G. Aspartame:

- It is a dipeptide (aspartic acid and phenylalanine) that serves as **sweetening agent**. It is used in replacement of **cane sugar**.

H. Atrial natriuretic peptide:

1. It is a peptide produced by specialized cells in the **heart** and **nervous tissue**.
2. It stimulates the production of **dilute urine** (opposite to vasopressin).

MCQ

8. The following amino acids have hydrophobic side chains, EXCEPT.
a- Tyrosine b- Alanine c- Leucine d- Valine

9. Imidazole ring is present in:
a- Arginine b- Tryptophan c- Histidine d- Proline

10. Which of the following amino acids has a non-polar side chain?
a- Serine b-Valine c- Asparagine d- Threonine

11. All the following are glucogenic amino acids, EXCEPT:
a- Glycine b- Serine c- Leucine d- Aspartic acid

12. Which of the following amino acids has a net physiological pH?
a- Glutamic acid b- Lysine c- Valine d- Leucine

13. Which is the ketogenic amino acid?
a- Alanine. b- Glutamic acid c- Leucine d- Aspartic acid

14. All the following are essential amino acids, EXCEPT:
a- tyrosine b- Lysine c- Valine d- Phenylalanine.

15. Non-essential amino acids:
a- Are not seen in tissue proteins b- Could be synthesized in the Body
c- Have no role in body metabolism d- Have aromatic ring structure

16. At isoelectric pH, the amino acids, and proteins show;
a- Maximum net charge b- Maximum mobility in electric field
c- Maximum precipitability d- Maximum buffering action

17. Enzymes are activated by phosphorylation of which amino acid residue:
a- Cysteine b- Serine c- Glutamic acid d- Lysine.

18. The following are aliphatic amino acids,
a- Alanine, valine, and glycine. b-Glycine, leucine, and serine.
c- Threonine, serine, and glutamic acid. d. Phenylalanine, tryptophan, and histidine.

19. All the following are heterocyclic amino acids, EXCEPT:
a- Histidine. b- Phenylalanine. c- Tryptophan d- Proline.

20. The following are basic amino acids:
a- Tryptophan and phenylalanine. b-Alanine and glycine.
c- Histidine, lysine, arginine. d- Valine, leucine, and isoleucine.

21. Non-polar amino acids include:
a- Glutamine and asparagine. b- Phenylalanine and tryptophan.
c- Cysteine, serine, and tyrosine. d- Lysine, arginine and histidine.

22. An essential hydroxy-containing amino acid is:
a- Tyrosine. b-Serine. c- Threonine. d-Hydroxy lysine.

23. Semi-essential amino acids include:
a- Valine and threonine. b-Arginine and histidine.
c- Cysteine and methionine. d-Phenylalanine and tyrosine.

Proteins

- **Nature of proteins:**

A. Composition:

1. Proteins are macromolecules formed of amino acids united together by **peptide bonds**.
2. Amino acids are commonly found in proteins in different proportions.
3. Some proteins are formed of 2 or more **polypeptide chains**.

B. Size of proteins.

1. Proteins having a **very high molecular weight**, ranging from 5,000 to several millions.
2. The term protein is applied to describe molecules **greater than 50 a.a.**
3. Molecules contain **less** than 50 amino acids are termed **peptides**.

- **Functions of proteins:**

1. **Enzymes:** Enzymes are protein
2. **Transport:** Of small molecules and ions e.g.
   a. Hemoglobin is a carrier for oxygen.
   b. Lipids are transported as lipoproteins.
3. **Structural elements: e.g.**
   a. **Cell membrane** contains proteins in the form of glycoproteins.
   b. **Skin and bone:** e.g. contains proteins in the form of collagen.
4. **Hormonal regulation:**
   a. Some hormones are protein in nature e.g. **growth hormone**.
   b. Cellular **receptors** that recognize hormones are proteins
5. **Defense mechanism:**
   a. **Antibodies:** (immunoglobulins) are protein in nature.
   b. **Keratin** found in skin and other tissues is protein that protect against mechanical and chemical injury.
6. **Blood clotting:** Coagulation factors are proteins.
7. **Storage:** as **ferritin** which is a storage form of **iron**.
8. **Control of genetic expression:** many regulators of genes are protein in nature.

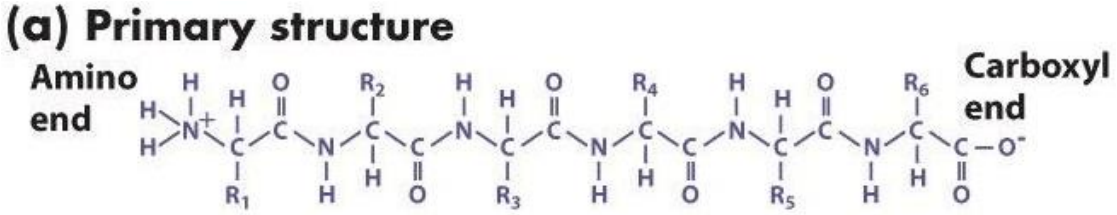
- **Conformation of proteins = (protein structure):**

A. Primary structure:

- **Definition:** It is the **arrangement** of amino acids in the **polypeptide** chain.
- **Bonds responsible for the primary structure:** The peptide bonds "covalent".
- **Mechanism:**

1. Each polypeptide chain starts on the left side by free amino group of the first amino acid, It is termed **N-terminal** (or **N-terminus**) amino acid.
2. Each .polypeptide chain ends on the right side by free carboxyl group last amino acid, It is termed **C-Terminal** (or **C-terminus**) amino acid.

3. The **remaining amino acids** in the chains are termed: **amino acid residues**
4. The types and arrangement of amino acid in each protein is determined by the **genetic information** present in **DNA**.

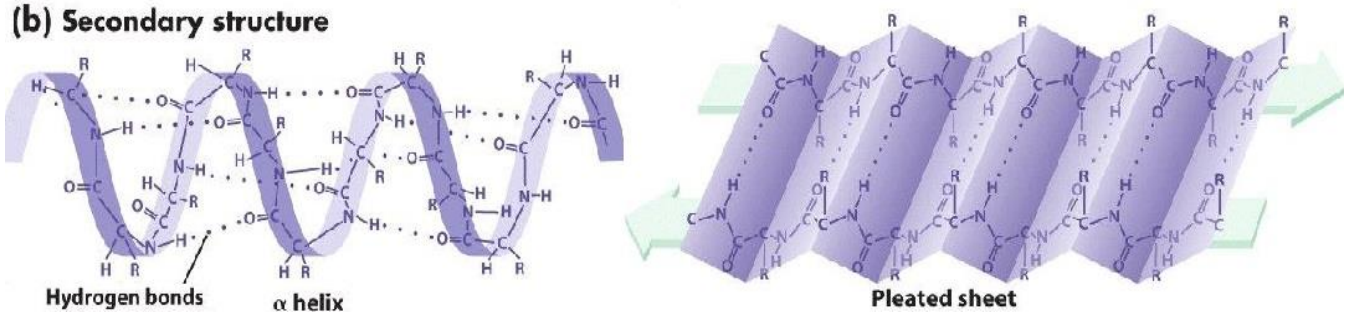


B. Secondary structure:

- **Definition:** It is the **spatial** relationship of adjacent **amino acid residues**.
- **Bonds responsible: Hydrogen bond**. It is the bond between the hydrogen of **-NH** group of one amino acid residues and the carbonyl oxygen **(C=O)** of the fourth one
- **Mechanism:**

1. Secondary structure results from **interaction of adjacent amino acid residues** (**first** and **fourth**).
3. There are **2** main forms of secondary structure **α-helix** and **β-pleated** sheets:

The α-helix	β-pleated sheets
- **Shape & formation:** It is a rod like structure with the peptide bonds coiled tightly inside and the side chains of the residues (R) extending outward from the chain. - **Characteristics:** 1) Each **(C=O)** of one amino acid is hydrogen bonded to the **(-NH)** of the next **fourth** amino acid in the chain (1→4) 2) The complete turn distance equals **54 nm.** 3) Each turn contains **3.6** amino acids residues.	- **Shape & formation:** a) This structure is formed between **two** or **more separate** polypeptide chains. It may also be formed between **segments** of the **same** polypeptide chain. b) **Hydrogen bond** is also responsible for its formation. It occurs between **(-NH)** group of **one** chain (or segment) and **(C=O)** of group of **adjacent** chain (or segment). - **Two types of β-sheets are present:** **1) Parallel β-sheets:** in which the two polypeptide chains run in the **same** direction. **2) Antiparallel β-sheets:** in which the two polypeptide chains run in **opposite** direction.



C. Tertiary structure:

- Definition: This is the **final arrangement** of a **single** polypeptide chain resulting from spatial relationship of more distant amino acid residues.

- There are two forms of tertiary structures:

a) Fibrous: which is an **extended** form e.g. keratin, collagen and elastin.

b) Globular: which is a **compact** form and results from folding of polypeptide chain e.g. myoglobin.

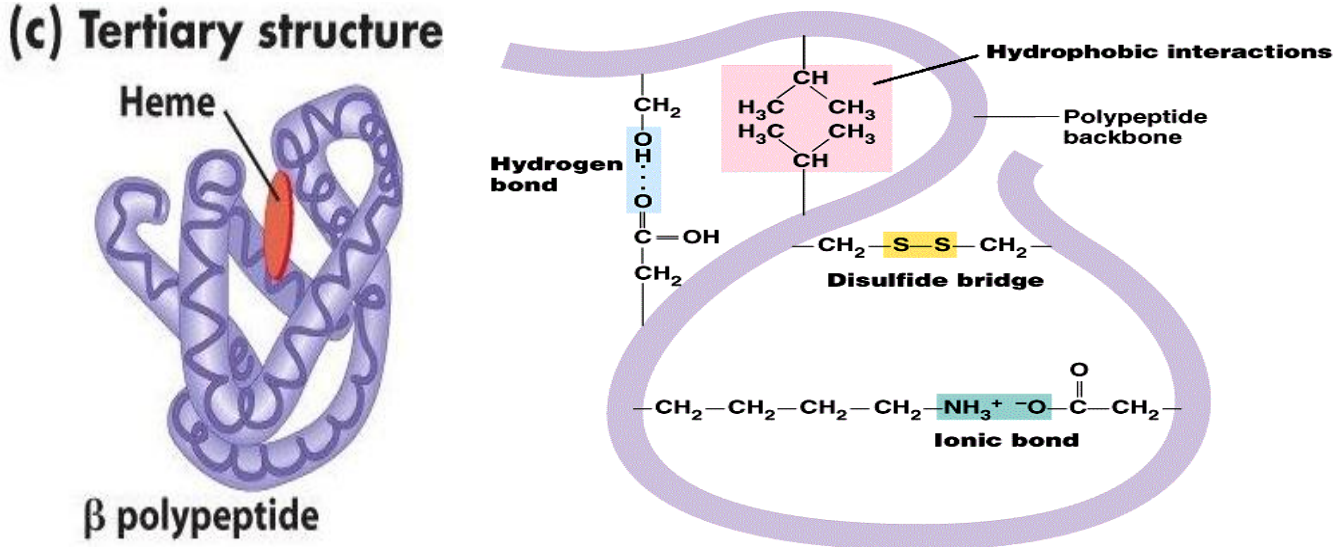
- Bonds responsible for tertiary structure are:

a) Hydrogen bonds: within the **chain** or between **chains**

b) Hydrophobic bonds: between the **nonpolar side chains** (R) of **neutral** amino acids.

c) Electrostatic bonds: (**salt bonds**): between **oppositely charged groups** in the side chains of amino acids e.g. **amino group** of lysine and **carboxyl group** of Aspartate.

d) Disulfide bonds: between **residues** within the chain.



D. Quaternary structure

- Many proteins are composed of several polypeptide chains. Each poly peptide chain is called: **subunits**. **Each subunit** has its own **primary, secondar**y and **tertiary** structure,

- Bonds responsible for quaternary structure:

a) Hydrogen bond.

b) Hydrophobic bond.

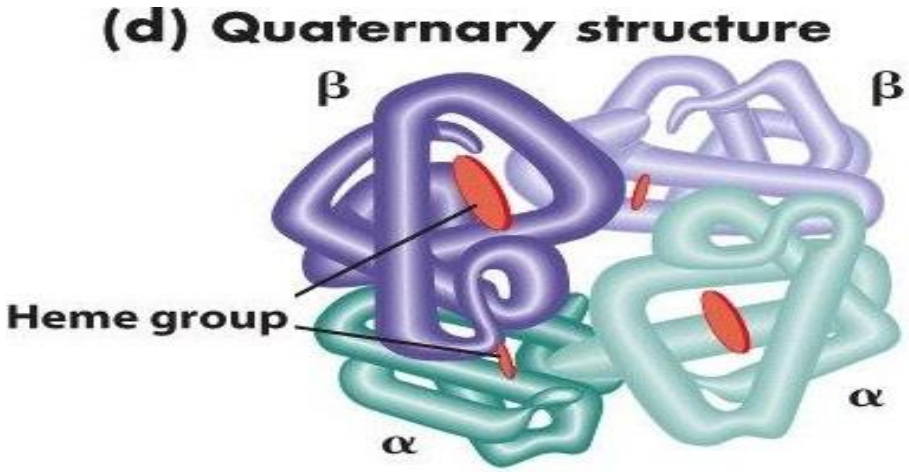
c) Electrostatic bond

- Examples of proteins having quaternary structure:

a) Insulin: 2 subunits.

b) Lactate dehydrogenase enzyme: 4 subunits.

c) Globin of hemoglobin: 4 subunits.



- **Denaturation**

A. Definition: unfolding and loss of secondary tertiary and quaternary structure.

- Does not affect primary structure i.e. not accompanied by hydrolysis of peptide bond.
- Denaturation may be **reversible** (in rare cases)

B. Effect of protein denaturation:

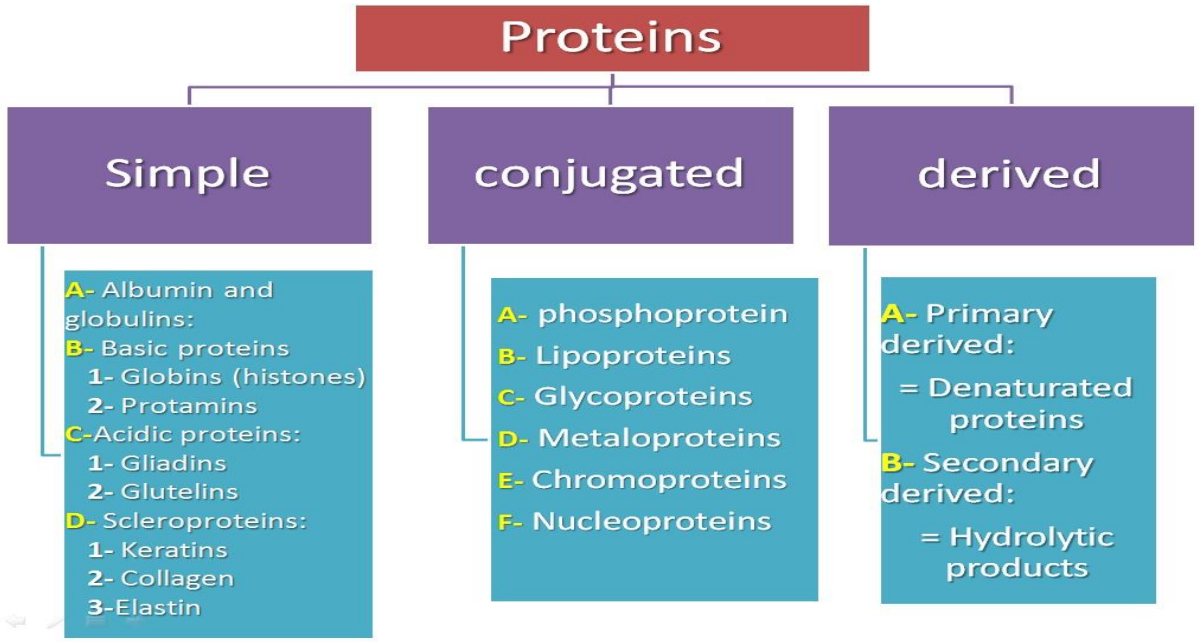
1. **Loss of biological activity**: e.g. insulin loses its activity after denaturation.
2. Denaturated protein are often **insoluble**.
3. Denaturated protein are **easily precipitated**.

C. Denaturating factors include:

1. **Heat:** causes coagulation and precipitation of certain proteins like albumin.
2. **Organic solvents:** They interfere with **hydrophobic bonds** of proteins.
3. **Detergents:** They contain both hydrophobic and hydrophilic groups i.e. amphipathic. They interfere with hydrophobic bonds of proteins.

4. **Strong acids or bases:** They lead to change in pH which affects the charges on polypeptide chains. As a result, hydrogen and electrostatic bonds will be disrupted.
5. **Heavy metals:** as **lead** and **mercury** salts:
   a) They form ionic bonds with negatively charged ions in polypeptide chains. This leads to disruption of electrostatic bonds.
   b) They unite with **-SH** (sulfhydryl) groups of proteins causing its denaturation (-S-Hg).
6. **Enzymes:** e.g. **Digestive** enzymes.
7. **Urea, ammonium sulphate and sodium chloride:** cause precipitation of proteins.
8. **Repeated freezing and thawing:** cause disruption of hydrogen and other bonds.

- **Classification of proteins**



➢ **Simple proteins,**

A. Albumin and globulins:

	Albumin	globulins
coagulated by heat	coagulable	Same
biological value	high	Same
Solubility	Soluble in water	Soluble in salt solution
Molecular weight	68.000	150,000
Precipitation	By full saturated ammonium sulphate	By half saturated ammonium sulphate
Sources: **1)Blood** **2)Milk** **3)Egg**	 Serum albumin Lactalbumin Egg albumin	 Serum globulins Lactglobulin Egg globulin

B. basic proteins: Globins (=**histones**) **and** protamines:

Both are basic proteins i.e. rich in basic amino acids.

	Globins (=histones)	Protamins
Type of basic amino acid	Histidine	Lysine and Arginine
Solubility	In salt solution	1. In salt solution 2. In 70% ethanol
Sources: **1. Combined with DNA** **2. Combined with Heme**	1. In plants & animals 2. To form hemoglobin	In fish

C. Gliadins and Glutelins:

1. Both are **acidic** proteins i.e. rich in acidic amino acids: **glutamic acid**.
2. Both are present in **cereals**
3. Both are soluble in diluted acids and alkalies. **Gliadins** also soluble in 70% ethanol.

D. Scleroproteins:

They include: keratin, collagen, elastin and reticulin.

1. Keratins:

a) Location: They are found in hair, nail, enamel of teeth, and outer layer of skin.

b) Structure: They are **α-helical polypeptide** chains. They are rich in **cysteine** (which provides **disulfide bonds** between adjacent polypeptide chains).

c) Solubility: It is **insoluble** due to their high content of **hydrophobic a.a**

2. Collagen

a) Types of collagens:

- There are more than **12** types of collagen. Type **I** is the most common in human body (**90%**) of cell collagens.
- Collagens form about **30%** of total body proteins.

b) Functions and Location:

- It is the protein of connective tissue present in **skin**, **bones**, **tendons** and **blood vessels.**
- Bones and teeth are made by adding **mineral** crystals to the collagen.
- Collagen may be present as a **gel** e.g. in **extracellular matrix** or in **vitreous humour of the eye.**

c) Structure:

1) Collagen molecules are simple protein; consist of **3** polypeptide chains called **α-chains**. They are twisted around each other forming triple helix molecule.

i- The 3 polypeptide chains are held together by hydrogen bonds
ii- each chains about 300 nm length and 1 .5nm in diameter.
iii- Each chain is formed of 1050 amino acids.

2) Amino acids composition acid sequence:

i- Amino acids composition: Collagen contains **33%** glycine (the smallest amino acid), **10%** proline, **10%** hydroxy proline and **1%** hydroxylysine.

ii- Amino acids sequence: Every **third** amino acid in the **α-chain** is glycine. The repeating sequence is glycine-X-Y, where X is frequently proline and Y is often hydroxy-proline or hydroxylysine.

4) Glycosylation: Collagens are present in the form of glycoprotein. Glucose and galactose are commonly attached to collagen

5) Collagen molecule has very firm structure due to:

i- Each helical turn contains only 3 amino acids. For other proteins, each turn contains 3.6 amino acids.

ii- **Glycine** (the smallest amino acid) forms 33% of total molecule. This makes the polypeptide chains **compact**.

iii- The high content of hydroxyproline and hydroxylysine increase the number of hydrogen bonds.

d) Collagen synthesis:

1. Collagens are formed by **connective tissue** cells called **fibroblasts.**
2. **Intracellular location:** The polypeptide chains of preprocollagen are synthesized on the rough endoplasmic reticulum, where **preprocollagen** is cleaved → **Procollagen** + Signal **(pre)** sequence.
3. Proline and lysine residues are **hydroxylated** by a reaction that requires O_2 and **vitamin C**
4. Glycosylation by glucose and galactose that added to hydroxylysine residues.
5. The Procollagen (in the form of triple helix) is secreted from the cell and cleaved → **Collagen**
5. **Cross links** are produced.

e) Solubility and denaturation:

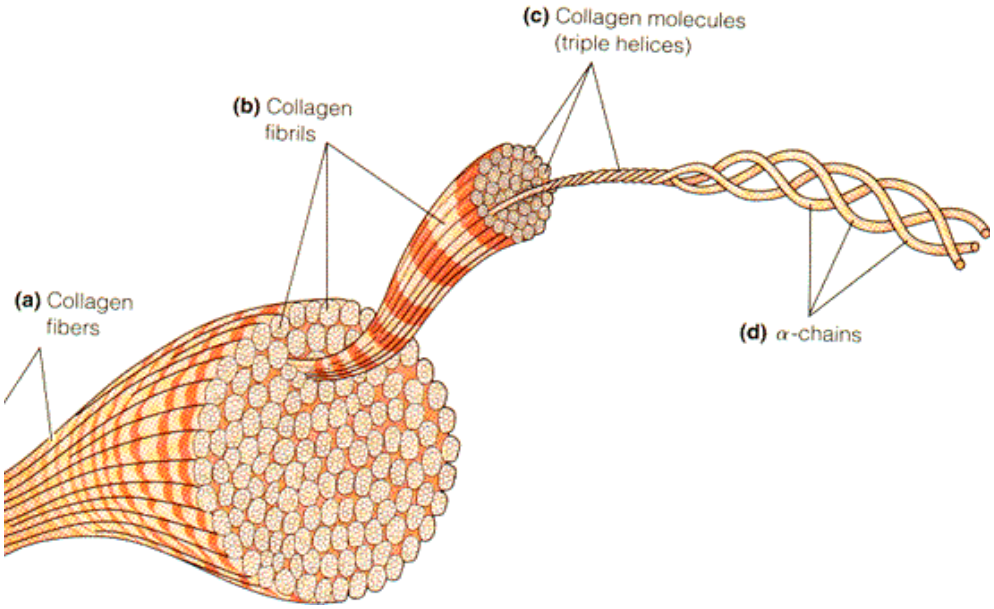
1) Solubility: Collagen is **insoluble** in **all solvents**. It is protein of low biological value and **not** digestible.

2) Denaturation:

- When collagen is heated, it loses all of its structure. The triple helix unwinds and the chains are separated. Then when this Denaturated mass cools down, it soaks up all of the surrounding water like sponge, **forming Gelatin**.
- **Gelatin** is **soluble** in water and **digestible**.
- **Gelatin** is given for patients during **convalescence** (in the form of **jelly**).

f) Collagen diseases: (Scurvy):

i- It is due to a **deficiency** in ascorbic acid (**vitamin C**). See vitamins.



3. Elastin:

a) Characters:

- It is connective tissue protein. It is **rubber** like **i.e.** it can be stretched to several times as their normal length, but **recoil** to their original shape when the stretching force is **relaxed**

b) Location:

It is present in **lungs**, the **walls of large blood vessels** and **elastic ligaments**.

C) Structure:

1) Elastin is formed of **4** polypeptide chain.
2) Elastin is similar to collagen, being rich in glycine (**1/3 of its a.a**) and **proline**. It is poor in hydroxyproline hydroxylysine.
3) The 4 polypeptide chains are interconnected through their lysine residues. The 4 lysine residues are linked together form a cyclic structure termed: **desmosine**.

Elastin is capable of undergoing 2 way stretch, due to its content of desmosine.

Role of α1-antitrypsin (α1-AT) in : elastin degradation:

1) **α1**-antitrypsin is an enzyme produced mainly by **liver**. It is also produced by blood cells **monocytes** and **macrophages**.
2) It is present in blood and other body fluids.
3) It inhibits a number of enzymes and destroys proteins.
4) Role of **α1-AT** in the lungs: In the normal lung, the alveoli are exposed to low levels of **elastase enzyme** released from **neutrophils**. Their proteolytic activity can destroy the elastin in alveolar walls: This elastase enzyme activity is inhibited by **α1**-antitrypsin.
5) Deficiency of **α1**-AT: Leads to destruction of connective tissue of alveolar walls by neutrophils elastase. This leads to lung disease called: **emphysema**.

	collagen	Elastin
Number of chains	3	4
Amino acids	1/3 glycine, rich in proline, more hydroxyproline,	1/3 glycine, rich in proline, less hydroxyproline and free from hydroxylysine
Structure	Fibrous	***Fibrous** in extended form ***Globular** in relaxed form
Direction of stretch	One direction	2 Directions due to presence of desmosine

- **Conjugated proteins:** On hydrolysis, they give protein (prosthetic group).They include: part (apoprotein) and nonprotein part

A. Phosphoprotein:

1. These are proteins conjugated with **phosphate** group.
2. Phosphate is attached to **-OH** group of serine (phospho-serine) or threonine (phospho-threonine) present in protein part.
3. **Examples:**

   a) Casein: A milk proteins

   b) Vitellin: Present in egg yolk.

   c) Phosphoenzyme: Phosphorylation (addition of phosphate to an enzyme) may activate or inactivate enzyme according to its type.

B. lipoproteins

C. Glycoproteins and proteoglycans

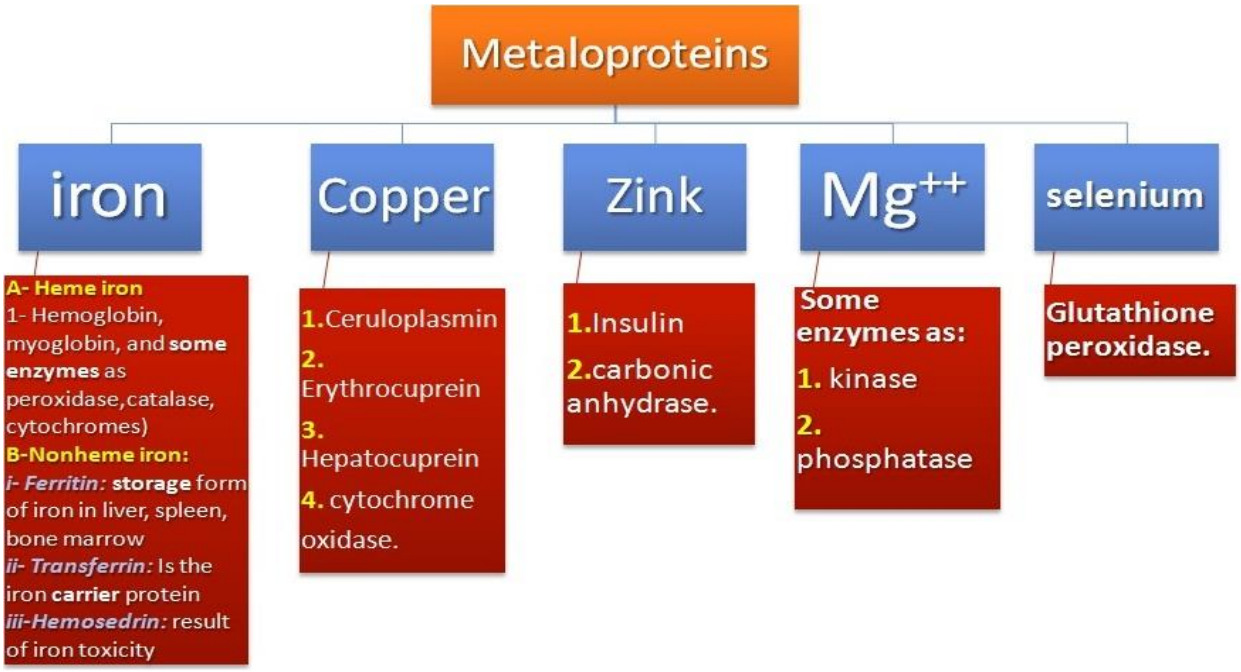
D. Nucleoproteins

E. Chromoproteins:

1. They are proteins conjugated with colored elements.

Metalochromoproteins (contain colored metal)	Non-metalochromoproteins (contain colored pigment)
1- All iron containing proteins (red) **2-All copper containing proteins (greenish blue).**	1- Flavoprotein (yellow) contain Flavin pigment e.g. FAD. 2- Carotenoids: they give vitamin A. 3- Melanoproteins: (brown to black) e.g. melanin pigments of hair and iris.

F. Metaloproteins: These are proteins conjugated with **metals**



G. Hemoproteins

- **Definition:** Hemoproteins are conjugated protein formed of protein part (globin) and nonprotein prosthetic part (Heme).

1. Hems containing iron (red in color). Thus hemoproteins are considered Metaloproteins.

2. Hemoproteins include many **biologically active compounds as:**

a) Hemoglobin: This carries oxygen.

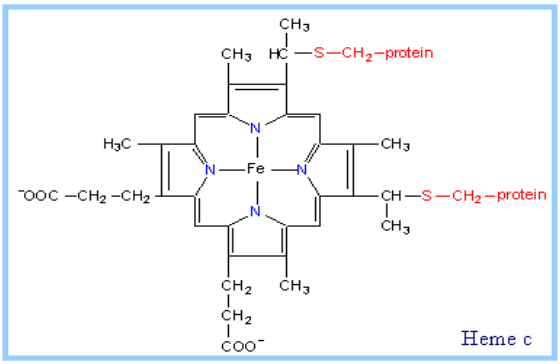
b) Myoglobin: This stores oxygen in muscles.

c) Respiratory enzymes: These use oxygen.

- **Structure of Heme:**

1. Four Payrol rings are united together to form **protoporphyrin III**.

2. Iron in ferrous state **(Fe^{++})** is incorporated in protoporphyrin III to form **heme**.



- **Hemoglobin:**

1. It is a Metaloproteins formed of heme and globin.

- Globin is a globular protein rich in **histidine** amino acids. It forms about of 95% of haemoglobin molecule.
- Globin is a protein having a **quaternary** structure. It is formed of **2 α chain** (each 141 amino acids) and **2 β chains** (each 146 amino acids).

Functions of hemoglobin:

1. Carries O_2 to tissues and removes CO_2 from them to the lungs.
2. Acts as blood buffer.
3. Synthesis of heme.
4. Structure of hemoglobin.
5. Properties of hemoglobin.
6. Hemoglobin derivatives.

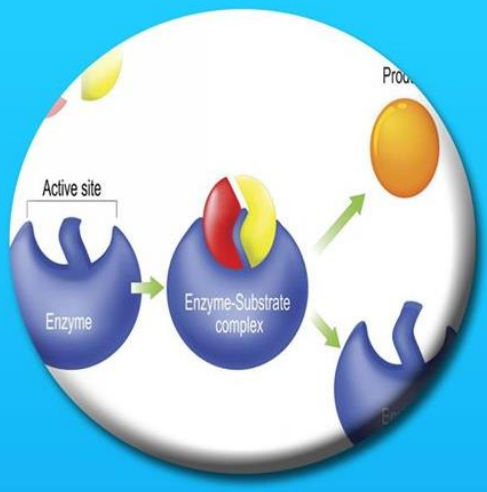
- **Myoglobin**

1. It is found only in the cytosol of **red skeletal muscle** and **cardiac muscle**. It gives these tissues their characteristic red color.
2. It is formed of one heme molecule attached to one polypeptide Globin.
3. Myoglobin has much **higher affinity** for oxygen than hemoglobin. It is unable to release it except under very low oxygen tension.
4. Myoglobin concentration is increased in blood in **myocardial infarction**.

- Clinical aspects:

1. **Myoglobinuria**
   a) It is the release of myoglobin from muscles after massive crush injury.
   b) Myoglobin is excreted in urine, colors it **dark**. It may cause renal tubular obstruction and **renal failure**.
2. **Plasma myoglobin is increased following myocardial infarction, but measurement of** serum myocardial enzymes provides a more sensitive index of myocardial infarction.
3. **Sickle cell anemia:**
   a) The blood cells of these patients contain abnormal hemoglobin called hemoglobin S (**HbS**).
   b) A molecule of HbS contains 2 normal α-chains and 2 mutants - chains in which glutamate at position six has been replaced by valine.
4. **Thalassemias:** Are anemias characterized by reduced synthesis of either alpha chain (**α-Thalassemias**) or beta chain (**β-Thalassemias**) of hemoglobin.

CHAPTER 4



Enzyme

E N Z Y M E S

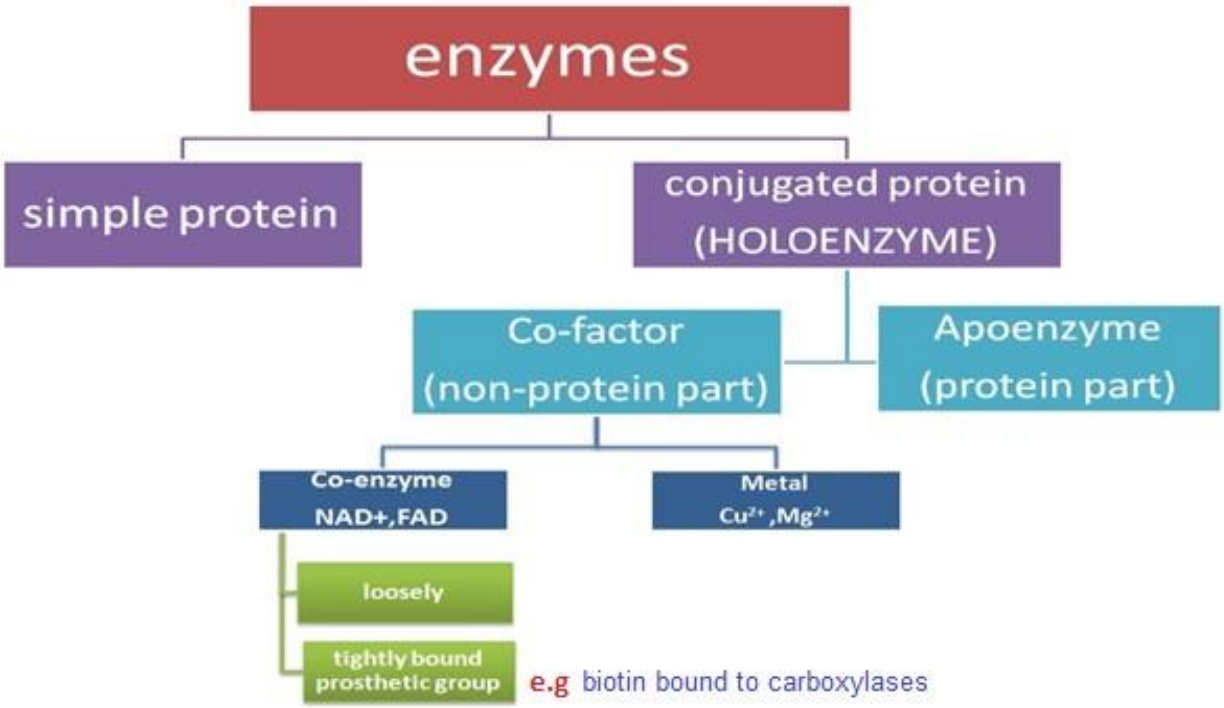
- **Definition:** These are **specific protein catalysts** that **accelerate** the rate of chemical reactions.
  - Enzyme structure is not changed by entering the reactions.
  - Enzyme does not affect the equilibrium constant (i.e. end products) of the reactions.
- **Cellular distribution of enzymes:**
  A. Intracellular enzymes: Produced and act inside the cells e.g. metabolic enzymes.
  B. Extracellular enzymes: Produced inside the cells and act outside the cells e.g. digestive enzymes.

Properties of ENZYMES

- The general properties of enzymes are those of proteins:

1. They are globular proteins.
2. They can be denatured by physical and /or chemical agents and they loose their biological function as the denaturation change their conformation.
3. Enzymes are usually specific in action and the specificity varies in degree (see later).
4. Some enzymes are simple proteins, others are conjugated proteins.
5. Each enzyme has a characteristic tertiary structure and undergoes a conformational change suitable to the specific substrate
6. Some enzymes are secreted as proenzymes (zymogens) then they are activated at the time of action.

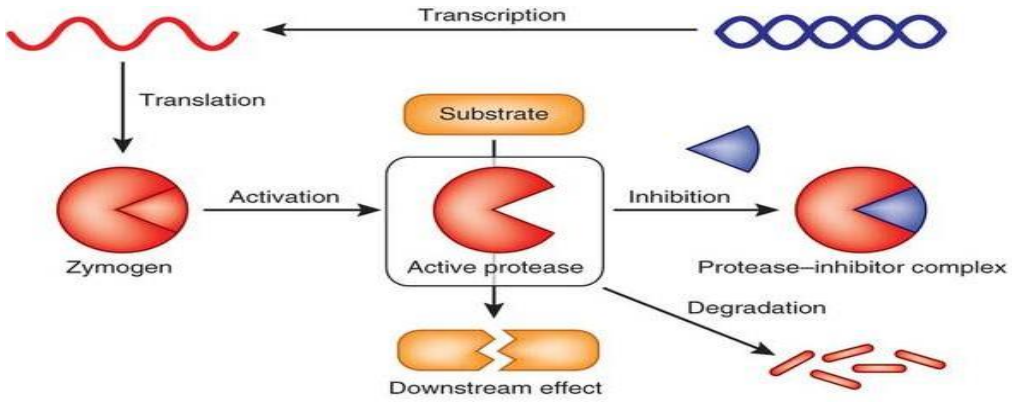
ENZYME STRUCTURE



Zymogens

They are **inactive enzymes**.

1. Zymogens are inactive because their catalytic sites are masked by a polypeptide chain.
2. Activation of zymogen, into active enzyme is done by removal of the polypeptide chain to open the catalytic site for its substrate.
3. **Examples** of zymogens: are pepsinogen and trypsinogen.



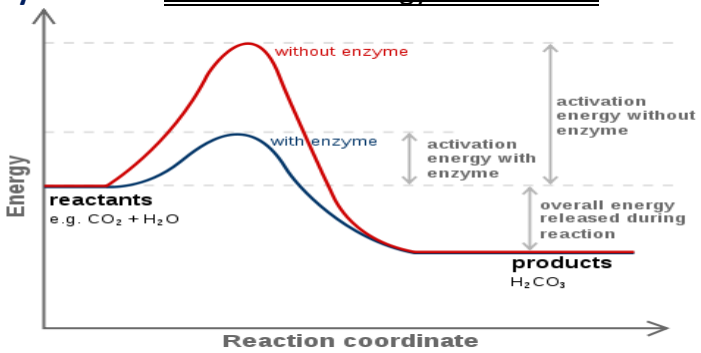
ENZYMES SPECIFICITY

1. **Relative specificity:** One enzyme acts on **compounds having the same type of bonds** e.g. lipase enzymes act on different TAG
2. **Group specificity:** the enzyme acts on a **special type of bond at specific site** and attached to **specific groups** e.g.:
   - **Pepsin:** acts on peptide bonds between amino group of **aromatic** amino acid and carboxylic group of another amino acid.
   - **Trypsin:** acts on peptide bonds between carboxylic group of **basic** amino acid and amino group of another amino acid.
3. **Optical specificity:**
   - Enzymes act on D or L isomers e.g.
     D - Amino acid oxidase acts only on D-amino acids
     L- Amino acid oxidase acts only on L-amino acids
   - Enzymes act on specific type of linkages according to the type of linkage (α or β) of the compounds attached to it e.g.
     α Amylase hydrolyses α-1-4 glycosidic linkage of starch.
4. **Absolute specificity:** One enzyme acts only on **one substrate** e.g. urease enzyme acts only on urea.

MECHANISM OF ENZYME ACTION

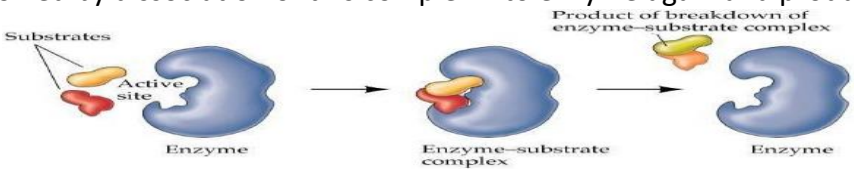
A. Energy of activation:

- All the reactions that proceed from initial substrates (**initial** state) to products (**final** state) consume energy. This is called **free energy** of the reaction.
- However the substrates do not become products directly, but must be **energized** (absorb energy) to reach an activated or **transition** state. This energy is called **activation energy**.
- At transition state, there is a high probability that a chemical bond will be made or broken to form the product.
- **The definition of activation energy:** is the amount of energy required to raise **1** mole of substance to the **transition state**.
- **The effect of enzymes:** is to **decrease** the energy of activation.



B. Active site:

1) During the enzyme action, there is a temporary combination between the enzyme and its substrate forming enzyme-substrate complex.
   This occurs at **active site of enzyme**.
2) This is followed by dissociation of this complex into enzyme again and products.

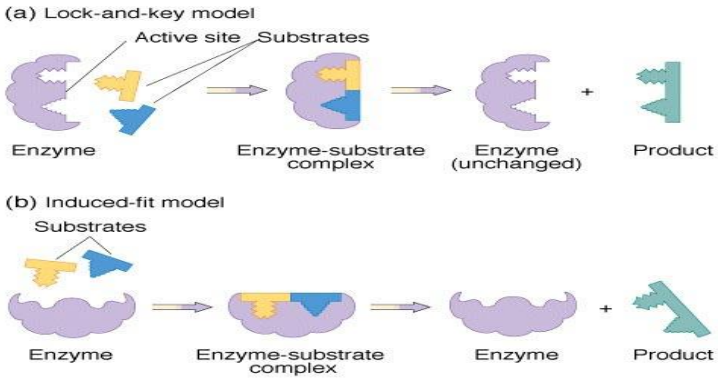


C. Theories of enzyme action:

Two theories have been proposed to explain the specificity of enzyme action:

a) The lock and key theory: The active site of the enzyme is complementary in conformation to the substrate so that enzyme and substrate "recognize" one another.

b) The induced fit theory: The enzyme changes shape upon binding the substrate, so that the conformation of substrate and enzyme protein are only complementary after the binding reaction.



CLASSIFICATION OF ENZYMES

1- Oxidoreductases (redox enzymes)	Oxidases Catalyze the removal of H or e^- from substrate but use only oxygen as a hydrogen acceptor and form **water** or H_2O_2 as a reaction product.	Oxidases forming water (H_2O): **e.g. cytochrome oxidase**
		2. Oxidases forming hydrogen peroxide (H_2O_2). They are **flavoproteins** containing either FMN or FAD
	Hpdroperoxidase Enzymes utilizing H_2O_2 as substrate.	**Catalase:** is present in all cells and tissues, especially liver, kidney and erythrocytes. In the catalase reaction, one molecule of H_2O_2 act as a **substrate** and the other molecule act as hydrogen donor.
		Peroxidase: present in RBCs, milk and leucocytes. Peroxidase uses H_2O_2 as substrate and an **organic substrate** as hydrogen donor. e.g. ascorbic acid, glutathione
	Dehydrogenases These remove hydrogen from one substrate to a hydrogen carrier. They cannot use oxygen as a hydrogen acceptor.	**a)** Dehydrogenases depend on **nicotinamide coenzymes** (NAD, NADP)
		b) Dehydrogenases depend on **riboflavin coenzymes** (FAD and FMN).
	Oxygenase They catalyze the direct incorporation of oxygen into the substrate.	**Dioxygenases:** Two atoms of oxygen molecule are incorporated into the substrate. As in tryptophan metabolism **Mono-oxygenase:** Only one atom of molecular oxygen is incorporated into the substrate in the form of hydroxyl group (termed hydroxylases or mixed function oxidases), they require a hydrogen donor
2- Transferases **These are enzymes which catalyze transfer of functional groups (G) other than hydrogen**	Transglycosylases (glycosyl transferases):	They catalyze transfer of an activated glycosyl (sugar) residue. Usually activation by UDP glucose
	Transphosphorylases (phosphotransferases):	They catalyze transfer of phosphoryl group 1. kinases 2. phosphoglucomutases
	Transacylases (acyl transferases)	They catalyze transfer of acyl group (R-CO) and they need coenzyme A (COA) as a carrier for acyl group
		These transfer NH_2 group from amino acid to

	Transaminases	α-ketoacid to produce a new amino acid, vitamin B_6 is a coenzyme
	Transmethylases (methyltransferases)	These transfer one carbon e.g. CH_3 group from methyl donor to methyl acceptor. The methyl donor is mainly S-adenosyl-methionine. The methyl carrier is methyl tefrahydrofolic acid ; and methyl-cobalamine
3- Hydrolases **These enzymes act by splitting (cleavage) of a certain bond by adding water.**	Glycosidases. act on glycosidic linkage causing its separation by hydrolysis	Amlyases α 1,4 glucosidase): Starch maltose
	Esterases These attack the ester linkage i.e. (linkage between acidic and alcoholic group)	Lipase: Triglyceride Glycerol + 3Fatty acids
	Peptidases **Split** the peptide linkage (CO-NH) of proteins.	**Endo-peptidase:** These act on intenal bond in the polypeptide chain e.g.: pepsin.
		Exo-peptidase: They are divided into: Carboxypeptidase: act on the carboxylic end Aminopeptidase: act at the amino end of protein chain.
4. Lyases:	These catalyze the addition or removal of groups e.g. H_2O , NH_3 or CO_2, **without hydrolysis, oxidation or reduction**.	**Dehydratases (or hydratases)**: they catalyze removal or addition of water or from the substrate.
		Decarboxylases. They catalyze splitting of CO_2.
5. Isomerases	They catalyse the interconversion of two isomers.	Aldose-ketose isomerases
6. ligases	These enzymes link two molecules using **energy from ATP**	(1) Amide synthetase: (C —N) (2) Carboxylase:

COENZYMES

1- According to the structural basis into:

A- Vitamins Coenzymes:

Vitamin	Coenzyme derivative	Group carried in activated form
Thiamine (vitamin B1)	Thiamine pyrophosphate(TPP)	Aldehyde
Riboflavin (vitamin B2)	Flavin adenine dinucleotide Flavin mononucleotide (FAD, FMN)	Hydrogen carrier
Nicotinate (niacin)	Nicotinamide adenine dinucleotide, Nicotinamide adenine dinucleotide	Hydrogen carrier
Pyridoxine, pyridoxal Pyridoxamine (vitamin B6)	Pyridoxal phosphate(PLP)	Amino group
Pantothenic acid	CO enzyme A	Acyl group
Biotin	Carboxbiotin	CO_2
Folate	Tetrahydrofolate(THFA)	One carbon unit
Cobalamin (vitamin B12)	Cobamide coenzymes	- Methylcobalamine - Deoxyadenosylcobalamine
Lipoic acid	Lipoamide	Acyl group, Hydrogen carrier
Quinone	Ubiquinone	Electrons
Vitamin C	L- ascorbic acid	Hydrogen carrier

B- Non Vitamins Coenzymes:

1- Nucleotide coenzymes (UDP-glucose, others nucleotide derivatives of carbohydrates): ATP.
2- Nucleoside: S adenosyl methionine (SAM) .
3- Peptide coenzymes (glutathione :GSH)

2- According to the functional basis into:

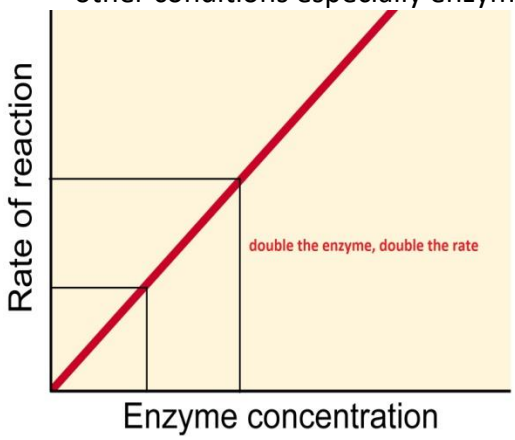
Coenzymes for transfer of H Hydrogen carriers	Coenzymes for group transfer Other than H
1. NAD+ and NADP+ **3. Lipoic acid** **5. Vitamin C** **2. FMN and FAD** **4. Coenzyme Q** **6. Glutathione.**	**1. ATP, GTP, CTP etc.** **2. Thiamin pyrophosphate (TPP).** **3. Coenzyme A (CoA)** **5. Folic acid** **4. Pyridoxal phosphate (B_6)** **6. Biotin**

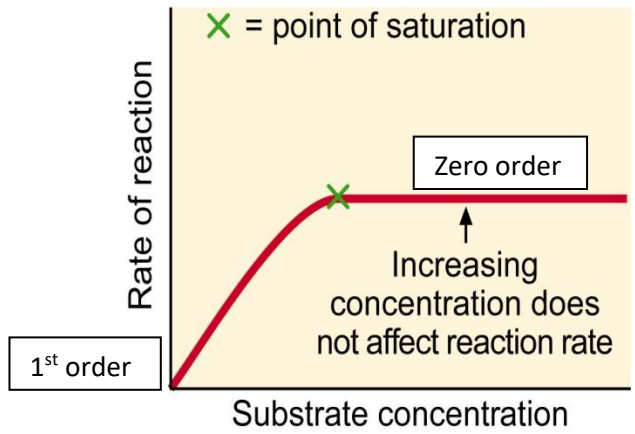
FACTORS AFFECTING ENZYME ACTIVITY

1. Concentration of enzyme: The initial velocity of a reaction is **directly proportional** to the amount of the enzyme present, provided that all other conditions remain constant.

2. Concentration of substrate:

The initial velocity of a reaction is **directly proportional** to the amount of substrate present **till** it reaches a **maximum point** known as **maximum velocity** (Vmax), where any further increase in the amount of substrate causes **no** increase in the velocity of the reaction. This is true if all other conditions especially enzyme concentration remain constant.

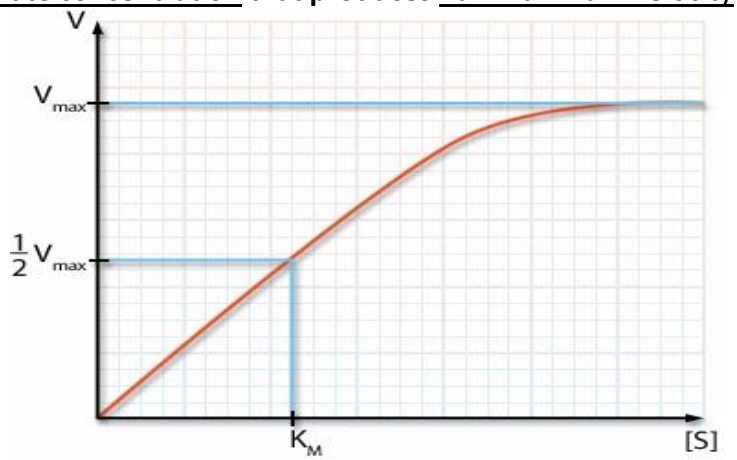




a) Definition of maximum velocity (V max): It is the maximum point in substrate velocity curve where any further increase in the amount of substrate causes no increase in the velocity of the reaction **due to** enzyme saturation.

c) Michaelis constant Km

- Def: It is substrate concentration that **produces** half maximum velocity.



d) Important conclusions about Michael is-Menten kinetics:

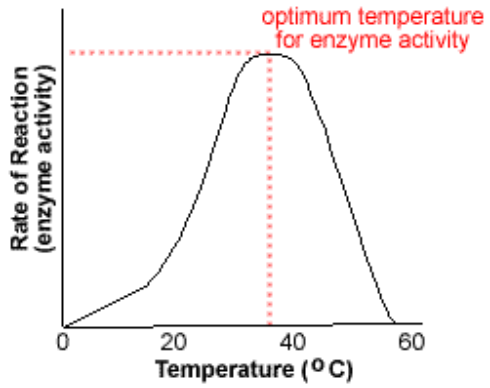
- K_m is a constant, characteristic of an enzyme and a particular substrate. K_m reflects the affinity of the enzyme for the substrate.
- The smaller the Km value → the more active the enzyme:
  - **i- Small (low) Km** reflects a high affinity of the enzyme for substrate i.e. low concentration of substrate is needed to half saturate the enzyme.
  - **ii- Large (high) Km reflects** a low affinity to the enzyme for substrate i.e. high concentration of substrate is needed to half saturate the enzyme.

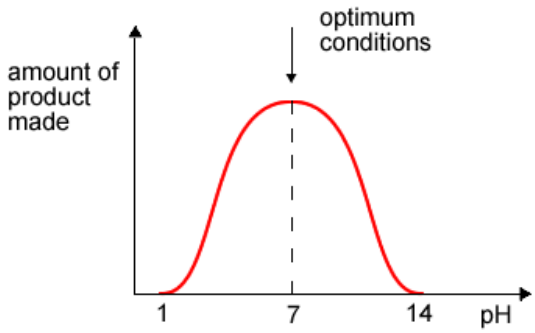
3. Effect of temperature:

- The optimal temperature for enzymatic activity in human body is **37 °C** i.e. the temperature of the cells.
- At **zero** temperature, the enzyme is **inactive**. The reaction velocity increases with increase of temperature until a maximum velocity is reached.
- Further elevation of the temperature results in a decrease in reaction velocity. At 55°C - 60°C, most enzymes are denaturated and become permanently inactive.

4. Effect of pH:

- The optimal pH for enzyme activity is that pH at which the enzyme acts maximally.
- Above or below this pH, the ionic state of both enzyme and substrate will be changed, and the rate of reaction will therefore decrease.
- Each enzyme has its **own optimal pH** e.g.
  - Salivary amylase 6.8.
  - Pepsin 2
  - Trypsin 8
  - Alkaline phosphatase 8.4
- Extremes of pH can also lead to denaturation of the enzyme.





5. Effect of Co-enzymes concentration:

- Co-enzymes concentration has the same effect and gives the same curve of substrate concentration on enzymatic activity, as NAD .

6. Effect of physical agents:

- Red and blue lights increase the enzyme activity.
- Heating, shaking stirring inhibit enzyme activity by denaturation.
- Ultra violet rays and infrared rays inhibit enzyme activity.

7. Effect of time;

- In all the previous factors, time must be taken into consideration, and its effect on enzyme kinetics must be measured against time.

8. Effect of product concentration:

- Increased product concentration decreases enzyme activity, this may be due to:
  1. Change in the pH of the medium.
  2. The product is more or less similar to the substrate, so it may compete it to catalytic site of the enzyme
  3. The product may bind to the enzyme at the allosteric Site (in case of allosteric enzyme).

9. Enzyme activators:

- Activators increase the rate of enzyme catalyzed reactions.
- Velocity of the reaction depends on activator concentration.
- Some enzymes are activated by different ways:

A. Removal of peptide converts inactive forms of the enzyme (zymogen) to active.

e.g. pepsinogen $\xrightarrow{\text{Pepsin or HCl}}$ pepsin.

B. Some enzymes containing SH groups e.g. glyceraldehyde 3-P dehydrogenase require reducing agents (vitamin C) to be activated.

C. Some enzymes require minerals, they are called metal activated enzymes eg.

- Cl^- for amylases (non metal ions) - Mg^{++} for kinases

D. Allosteric activators (Allosteric modifiers): The binding of allosteric activator produces conformational changes in the protein structure of the enzyme resulting in increased velocity of the reaction

e.g. AMP is an allosteric activator of **phosphofructokinase** enzyme.

10. Enzyme inhibitors:

MCQ

1. Which of the following is NOT true regarding enzymes?

a- Enzymes are proteins and can be denatured.
b- Enzymes act at a very low concentration.
c- Enzymes will only react with one or a very small number of compounds.
d-Enzymes are very small molecules, much smaller than their substrates.

2. All the following statements are true with regard to enzymes,

a- Enzymes lower activation energy. b- They alter equilibrium of the reaction
c- They accelerate the chemical reaction d- Most of the enzymes are proteins in nature

3. Enzymes which are synthesized in inactive form are called:

a- Co-enzymes b- Apo-enzymes c- Lysozymes d. Pro-enzymes (zymogen)

4. All of the following enzymes are oxidoreductases EXCEPT:

a. Glutathione peroxidase. b. Dioxygenase.
c. Catalase. d. Aldolase.

5. An example of lyase is:

a- Glutamine synthetase b- Fumarase
c- Cholinesterase d- Amylase

6. The enzyme belonging to the ligase class is:

a- Glycogen synthase. b- Glutamine synthetase.
c- Porphobilinogen deaminase. d- Histidine decarboxylmse.

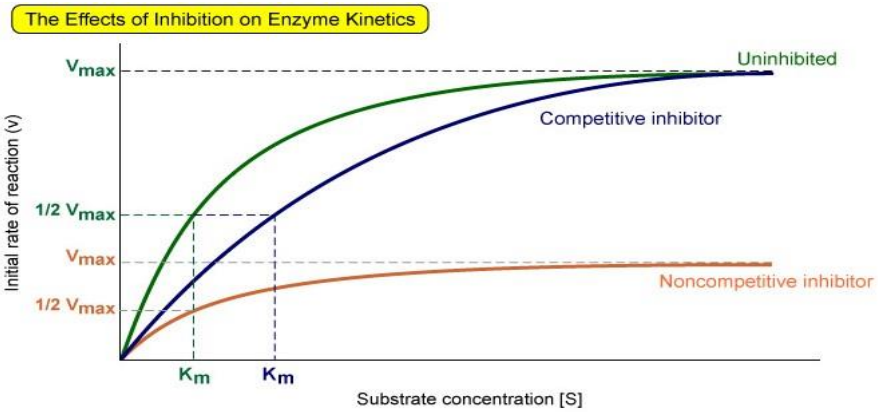
7. Coenzymes are:

a- Dialyzable, non-protein molecules. b- Colloidal protein molecules.
c- Structural analogues of enzymes. d- Different forms of the same enzyme.

Enzyme inhibitors

- **Definition:** These are substances that can diminish the velocity of enzymatic reactions.

Enzyme inhibitors		
Reversible inhibitors - Bind to enzymes through **non covalent** bonds. - Dilution of the enzyme-inhibitor complex dissociates the reversibly bound inhibitor and recovery of enz. activity.		**Irreversible inhibitors**
A. Competitive inhibitors	**B. Non-competitive**	
- **Similar** to substrate. - compete with substrate for **active site** of the enzyme. - Both substrate (S) and inhibitor (I) can bind with the catalytic site of the enzyme to form either **Enz-S-complex** or **Enz-I-complex**. - The combination between enzyme and substrate or inhibitor depends on: **1)** Concentration of substrate. **2)** Concentration of inhibitor. **3)** Affinity of both inhibitor and substrate to the active site of the enzyme. **- Example of competitive inhibitors:** **1)** Malonate and Succinate: both compete for the catalytic site of Succinate DH. **2)** Allopurinol and hypoxanthine: both compete on xanthine oxidase that oxidizes hypoxanthine into xanthine then to uric acid.. **3)** Dicumarol & Warfarin and vitamin K: both compete for the catalytic site of epoxide reductase enzyme. **- Effect of competitive inhibitor on Vmax and Km:** **a) Effect on Vmax:** A competitive inhibition **does not** affect Vmax. **b) Effect on K:** A competitive inhibition **increases** the Km of substrate.	- Inhibitor and substrate bind to different sites on the enzyme. - The inhibitor **does not** alter the catalytic site. - There is **no** structural similarity between substrate and inhibitor. - The inhibitor can bind either free enzyme or the enzyme-substrate complex. Both enzyme inhibitor complex and enzyme substrate inhibitor complex are inactive. **- Effect of noncompetitive inhibitor on Vmax and K:** a) Vmax is **decreased.** b) Km is **unchanged**.	-This type of inhibition cannot be reversed by adding more substrate - The inhibitor **alters** the catalytic site. - Irreversible inhibitors include the **following:** 1. All compounds that produce Denaturation of proteins. 2. Inhibitors of sulfhydryl group 3. Antienzymes: e.g. **Antithrombin III** 4. Removal of catalytic ions: by addition of EDTA. 5. Inhibition by phosphorylation and dephosphorylation 6. Cyanide and carbon monoxide inhibit cytochrome oxidase.

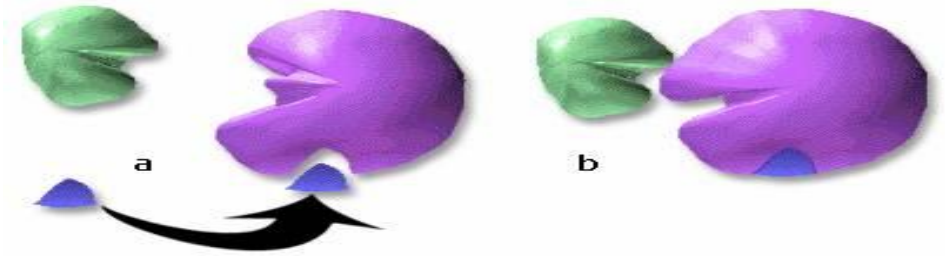


Regulation of enzyme activity

Enzyme activity is regulated by many mechanisms.

A. Allosteric regulation of enzyme activity:

1. Allosteric enzymes generally catalyze the irreversible steps in metabolic pathways.
2. The term allosteric means "other site", It indicates that a molecules called **effectors** (also called modifiers or modulators) can bind **non-covalently** at a site other than active site.



a) **Effectors** are positive if they **stimulate** catalytic reaction and negative if they **inhibit** the reaction.

b) Effectors may be the end product of a metabolic pathway. If it inhibits the reaction (negative regulation), it is called: **feedback inhibition**.

B. Feedback inhibition:

It means that the end product of a series of reactions directly inhibits the first enzyme of that series.

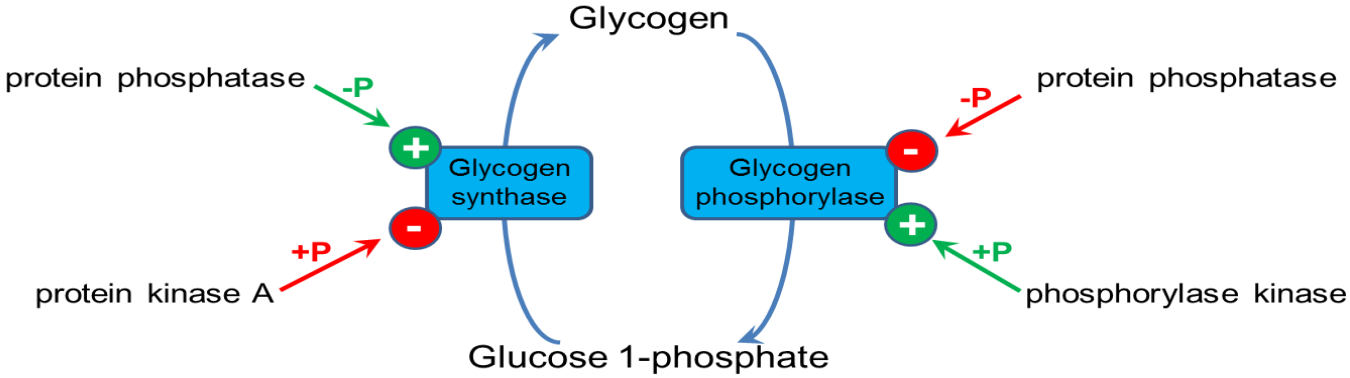
C. Feedback regulation:

It means that the end product of a series of reactions has ***no*** inhibitory effect on the first enzyme. It rather affects the **gene(s)** that code for the formation of that enzyme preventing its synthesis

D. Covalent modification: phosphorylation / dephosphorylation:

1. Some enzymes may be regulated by covalent modification, most frequently by the addition or removal of **phosphate** groups from the enzymes.
2. Phosphorylation reactions are catalyzed by a family of enzymes, called: **protein kinase**. It utilizes ATP as a phosphate donor.
3. Phosphate groups are removed from Phosphorylated enzymes by the action of **phosphoprotein phosphatase**

Example: glycogen synthesis/degradation



Isoenzymes

- **Definition:** Isoenzymes are different molecular forms of the enzyme that activate the same reaction, use the same coenzyme and same substrate but they are **different** in chemical protein structure. This **leads to:**
  1. Different **immunological** reactions.
  2. Different **Km** and **Vmax**.
  3. Different **physical properties**.
- **Example:**

1. Lactate dehydrogenase enzyme (LD)

- Is a tetramer i.e. contains 4 polypeptide chains. These 4 chains are a mixture of different proportions of 2 chains H and M (H. after heart & M after muscle).
- There are **5** isoenzymes of **LD** enzyme having a **Diagnostic importance:**

Determination of different isoenzymes helps in diagnosis of diseases e.g.

LDI_1	**HHHH**	**Heart**	Serum LDI_1 increases in certain heart diseases (myocardial infarction).
LDI_2	**HHHM**	**Red cells**	Acute leukemia
LDI_3	**HHMM**	**Lungs**	Acute leukemia
LDI_4	**HMMM**	**Other tissues**	
LDI_5	**MMMM**	**Liver**	Serum LDI_5 increases in certain liver diseases (infective hepatitis)

2. Creatine kinase (CK) (CPK):

- **CK-BB:** in brain.
- **CK-MB:** in Skeletal muscle.
- **CK-MM:** in myocardium.

3. Isocitrate dehydrogenase: (cytosolic & mitochondrial)

4. Phosphodiesterases: 1-5

CLINICAL IMPORTANCE OF ENZYMES

A- Diagnosis of diseases

- Enzymes are intracellular and when there is cellular damage, they are released into the circulation
- The measurement of these enzymes in the serum can be used in the diagnosis of certain diseases.

- **Enzymes in plasma are classified into:**

A. Functional plasma enzymes: These are enzymes present normally in blood to perform certain physiological functions. **They are characterized by:**

1. They are synthesized in the liver.
2. They are present in blood in higher concentration than tissues.
3. Their substrates are present in the circulation.
   - **Examples**: Proenzymes of blood clotting, lipoprotein lipase.

B. **Non-functional plasma enzymes:** These enzymes are present in a **very low** concentration in blood due to tissue turn over and increases in case of tissue damage.

They are characterized by:

1. They perform no physiological function in blood,
2. Their substrates, are absent from blood.
3. Their level is normally low and they increase in tissue damage
   - **Examples:** for these enzymes are:

1. **Alkaline phosphatase:** increases in obstructive jaundice, hyperparathyroidism, rickets and metastatic carcinoma to bone.
2. **Transaminases:**
   - Aspartate aminotransferase (AST) or glutamic oxaloacetic transaminase (GOT) increases in heart disease.
   - Alanine aminotransferase (ALT) or glutamic pyruvic transaminase (GPT) increases in liver diseases.

B- TUMOR MARKERS:

- **Definition of tumor markers:**
  - Tumor markers are macromolecules mostly proteins whose appearance or changes in concentration in blood or other body fluids is indicative to the presence, extent or progress of a malignant tumor.
  - Tumor markers may be tumor antigens, hormones or enzymes.
  - Alterations of serum enzymes in malignancy may be due to:
    1. Production of increased amounts of enzymes by tumor cells.
    2. Release of intracellular enzymes due to cell damage.
- **Enzymes used as tumor markers:**
  1. Alkaline phosphatase (ALP). It increases in bone metastasis.
  2. Creatine kinase (CK): The isoenzyme fraction of the brain (CKBB) diagnose breast tumors, prostatic carcinoma, colonic cancer, and transitional cell carcinoma of bladder.
  3. Lactic dehydrogenase (LDH). It is generally increased in malignancy.

- **Also decreased level of some enzymes can be used to** diagnose inborn errors of metabolism e.g.
  1. Glucose-6-phopshate dehydrogenase in **Favism**.
  2. Galactosyl transferase in **galactosemia**

C- Treatment of diseases:

- **Enzymes are used in treatment of some diseases e.g.**
  1. **Fibrinolysins** in treatment of infarctions (streptokinase).
  2. **Digestive enzymes** in treatment of maldigestion.
  3. **α-chymotrypsin** for treatment of intraocular haemorrhage.

MCQ

8. Which of the following causes a conformational change to the active site of an enzyme?

a- Proteolytic cleavage. b-Allosteric inhibitor.
c- Coenzymes. d- Competitive inhibitor.

9. In ……. inhibition, the inhibitor is an end product of the enzyme action

a- Non-competitive b- Allosteric
c- Competitive d- Feed back

10. The Km value of an enzyme is:

a- The substrate concentration at half maximal velocity.
b- Half the substrate concentration at maximal velocity.
c- Dissociation constant of enzyme-substrate complex.
d- The total enzyme concentration.

MCQ

11. In a competitive inhibition:

a- Km is increased and Vmax is increased. b- Km is decreased and Vmax is normal.
c- Km is increased and Vmax is normal. d- Km is decreased and Vrnax is increased.

12. All Of the following are true as regards isoenzymes

a- They have identical polypeptide chains. b- They have different affinities to the substrate.
c- They can be separated by electrophoresis. d-lhey are present in different cells.

13. Digestive enzymes belong to the class of:

a- Hydrolases. b- Ligases. c- Lyases. d- Oxidoreductases.

14. Concerning allosteric effectors:

a- Allosteric effectors are usually analogs of that substrate.
b- The allosteric site of an enzyme is distinct from its substrate binding site.
c- Allosteric effectors cause denaturation of the enzyme.
d- Allosteric effectors cause non conformational changes in the enzyme.

15. Which of the following metalloenzymes contain copper?

a- Superoxide dismutase b- Tyrosinase
c- Glutathione peroxidase d- Cytochrome oxidase

16. The enzyme:

a- Reduces the energy of activation. b- Increases total energy of substrate.
c- Increases the equilibrium constant. d- Decreases total energy of the product.

17. In competitive inhibition:

a- Inhibitor has structural similarity to substrate
b- Km is decreased
c- Vmax is decreased
d- Reaction rate is independent of substrate concentration

18. As regards lactate dehydrogenase, all are correct EXCEPT:

a- It is formed of four subunits. b- isoenzyme 5 increases in plasma in liver diseases.
c- there are 6 isoenzymes. d-isoenzyme I increases in plasma in myocardial infarction.

19. In inhibitors:

a- Km increases. b- Km decreases. c- Vmax decreases. d- All Of the above.

20. Elevation of the blood level of the following enzyme helps in the diagnosis of hepatitis:

a- Amylase b- Alanine transaminase c- Creatine Kinase d- Acid phosphatase

21. Isozymes are enzymes with different amino acid sequences but the same:

a- Tissue.
b- Function.
c- Quaternary structure.
d- Electrophoretic pattern.

CHAPTER 5

Carbohydrates Metabolism

INTRODUCTION TO METABOLISM

- Humans and all living organisms are in a steady dynamic state.
- This is maintained by the free energy obtained from the oxidation of nutrients through the different metabolic pathways.

- The objectives of this chapter are:
  1. To understand the **different forms of energy**.
  2. To know the **amount of energy stored in different types of chemical bonds**.
  3. To know **how chemical energy is generated, transferred and stored** by living cells.

METABOLISM

Metabolism means the series of biochemical reactions that occur for biomolecules in living organisms.

It is classified into: anabolism and catabolism.

ANABOLISM

- Means synthesis of macromolecules from simple one. Anabolism is usually endergonic (consumes energy).

Examples

- Synthesis of polysaccharides from monosaccharides.
- Synthesis of triacylglycerol from glycerol and fatty acids.
- Synthesis of proteins from amino acids.

CATABOLISM

Means breakdown of macromolecules into simplest components. It is usually exergonic (release energy).

- Catabolism of the main metabolites occurs in **4 stages:**

- In stage 1, metabolic fuels are hydrolyzed in the gastrointestinal tract to a diverse set of monomeric building blocks (glucose, amino acids, and fatty acids) and absorbed.
- In stage 2,
  - **THE** building blocks are degraded by various pathways in tissues to a common metabolic intermediate, **ACETYL-COA**.
  - Most of the energy contained in metabolic fuels is conserved in the chemical bonds (electrons) of acetyl-CoA.
  - A smaller portion is conserved in reducing nicotinamide adenine dinucleotide (NAD) to **NADH+H** or flavin adenine dinucleotide (FAD) to **$FADH_2$**.
  - Reduction indicates the addition of electrons that may be free, part of a hydrogen atom (H), or a hydride ion.
- In stage 3, the **citric acid** (Krebs, or tricarboxylic acid 'TCA') cycle oxidizes acetyl-CoA to CO_2. The energy released in this process is primarily conserved by reducing (NAD) to **NADH+H** or (FAD) to **$FADH_2$**.
- The final stage is **oxidative phosphorylation**, in which the energy of **NADH+H** and **$FADH_2$** is released via the **electron transport chain** (ETC) and used by an ATP synthase to produce **ATP**. This process requires O_2.

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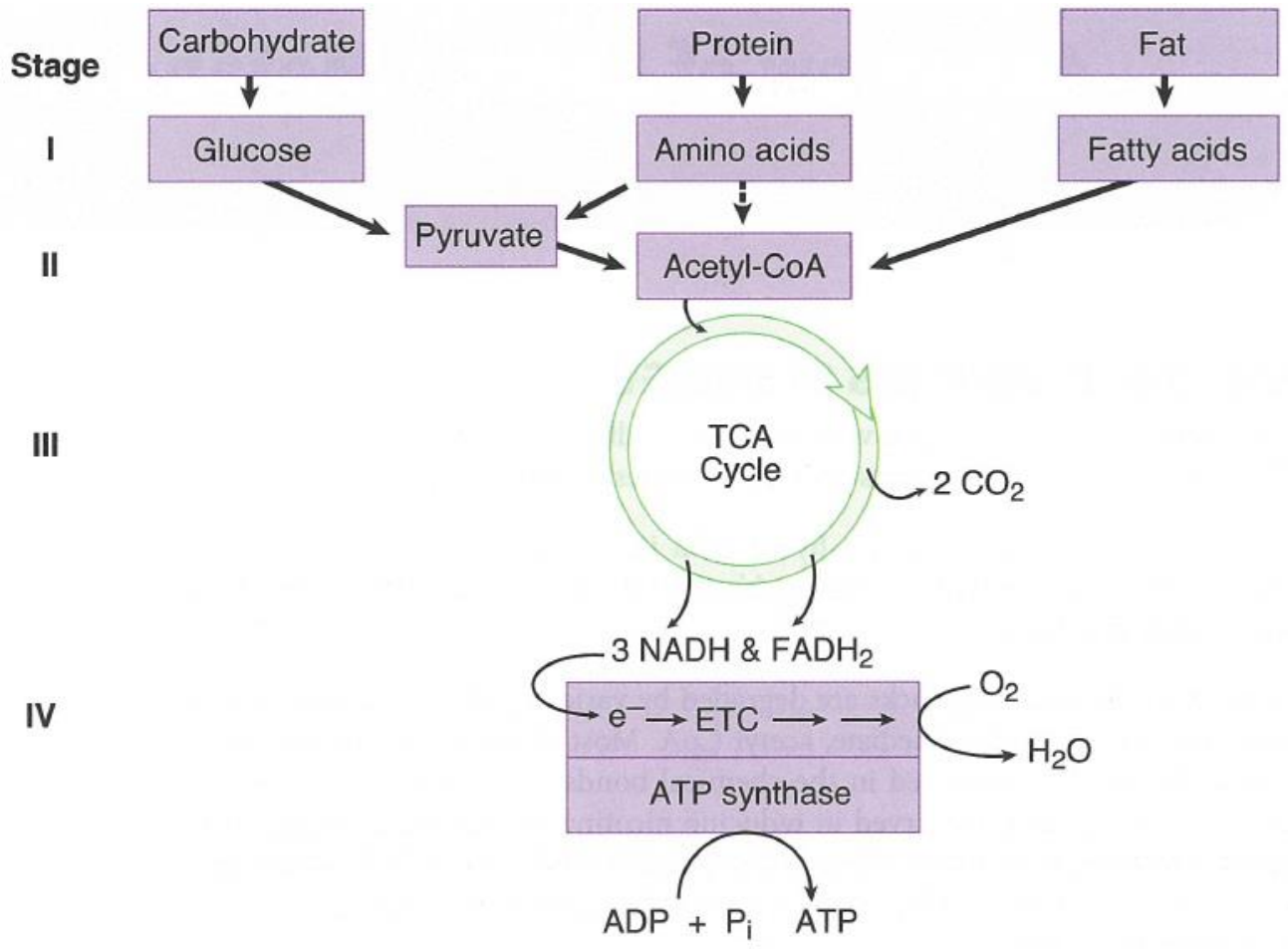

METABOLIC ENERGY STORAGE

- ATP is a form of circulating energy currency in cells. It is formed in **catabolic pathways** by phosphorylation of ADP and may provide energy for biosynthesis (**anabolic pathways**). There is a limited amount of ATP in circulation.
- Most of the excess energy from the diet is stored as **glycogen** and **fatty acids**. Although **proteins** can be mobilized for energy in a prolonged fast, they are normally more important for other functions (contractile elements in muscle, enzymes, etc.).

LOW AND HIGH-ENERGY BONDS

LOW-ENERGY BONDS yields < 7.3 Kcal/mol on hydrolysis.	HIGH-ENERGY BONDS yields > 7.3 Kcal/mol.
Examples of low energy bonds • Ester bonds (Phosphate ester) • Glycosidic bonds (oligo, polysaccharides) • Peptide bonds.	**1- Phosphate bonds** • Phosphoenolpyruvate. • Carbamoyl phosphate • Creatine phosphate • Pyrophosphate as ADP and ATP • 1,3 Bisphosphoglycerate **2- Sulfur bonds** • Active methionine: SAM • Thioester as acetyl COA • B-Ketoacyl-CoA as: **Acetoacetyl-Co**

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REDOX REACTION

Oxidation accompanied by reduction called redox reaction

OXIDATION	REDUCTION
1- Addition of oxygen 2. Removal of hydrogen 3. Loss of electron increase in positive charge. .	1. Removal of oxygen 2. Addition of hydrogen 3. Addition of electrons

Redox potential

Electron Affinity

Hydrogen is transferred through different component of redox chain so energy liberated is gradual

DEFINITION

Affinity of a substance for electron (its electronegativity) compared with hydrogen.

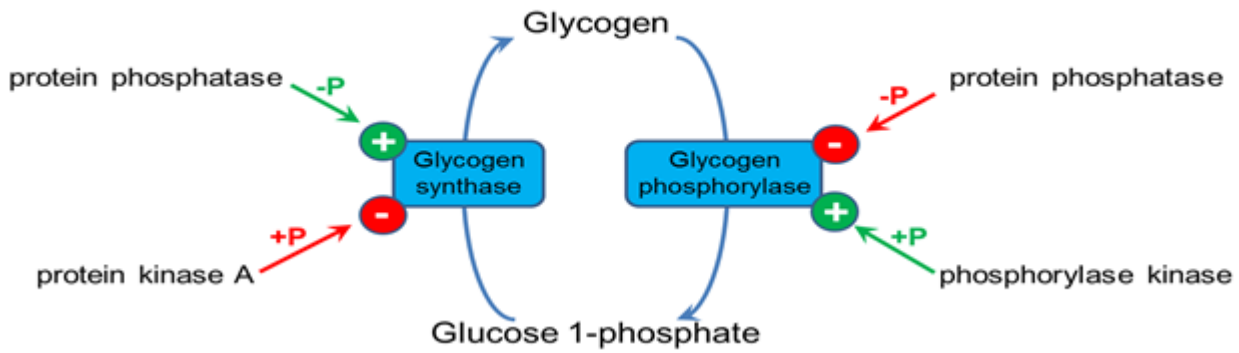
- Hydrogen has lowest electron affinity
- Oxygen has highest electron affinity.
- All other substances lie between O_2 and H^+.

NB. Hydrogen atom formed of one electron and one proton

REGULATION OF FUEL METABOLISM

- The pathways that are operational in fuel metabolism **depend on** the **nutritional status** of the organism. Shifts between storage and mobilization of a particular fuel, as well as shifts among the types of fuel being used, are very pronounced in going from the well-fed state to an overnight fast, and finally to a prolonged state of starvation. The shifting metabolic patterns are regulated mainly by the **insulin/glucagon** ratio.
- Insulin is an anabolic hormone that promotes fuel storage. Its action is opposed by a number of hormones (anti insulin hormones), including (glucagon, epinephrine, cortisol, and growth hormone).
- The major function of glucagon is to respond rapidly to decreased blood glucose levels by promoting the synthesis and release of glucose into the circulation.
- **Anabolic and catabolic pathways are controlled at three important levels:**
  - **Allosteric** inhibitors and activators of rate-limiting enzymes.
  - **Feedback inhibition.**
  - **Feedback regulation** "Control of gene expression" by **insulin, glucagon** and **substrate**.

Phosphorylation by (**glucagon**) through (**Kinase**) and de



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FATE OF GLUCOSE

Oxidation احرقه لو محتاج		***Storage*** أو أخزنه في التلاجات	***Conversion*** أو أحوله لحاجات
Major pathway	Minor pathway	As glycogen by glycogenesis in Liver and Muscles	e.g. - To lipid by lipogenesis or - To ptn
Glycolysis ↓ Pyruvate ↓ Acetyl Co-A ↓ Krebs cycle ↓ R. chain	- pentose phosphate pathway ***Or*** - Uronic acid pathway		

CHAPTER MAP

Glucose Metabolism		***Galactose Metabolism***	***Fructose Metabolism***
Feeding state واحنا واكلين هيكون في انسولين	**Fasting state** واحنا صايمين		
1- Glycolysis Glucose → pyruvate **2- Pyruvate → A. Co-A** **3- Krebs cycle** $NADH+H^+$ & $FADH_2$ **4- Respiratory chain** ATP **5- Minor pathways** PPP &UAP **6- Glycogenesis** **7- Lipogenesis** See lipid Metabolism	**1- Glycogenolysis** 2- **Gluco*neo*genesis**	**1- Conversion of Glucose to Galactose** **2- Conversion of Galactose to Glucose** **3- Lactose synthesis** ~~**4- Ds**~~	**1- Catabolism** **2- Conversion of Fructose to Glucose** ~~**3- Ds**~~

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GLYCOLYSIS (EMBDEN MEYERHOF PATHWAY)

DEFINITION

Breakdown of glucose into **2** molecules of **pyruvate aerobically** (in the presence O_2) or **2** molecules of **lactate an aerobically** (in the absence of O_2).

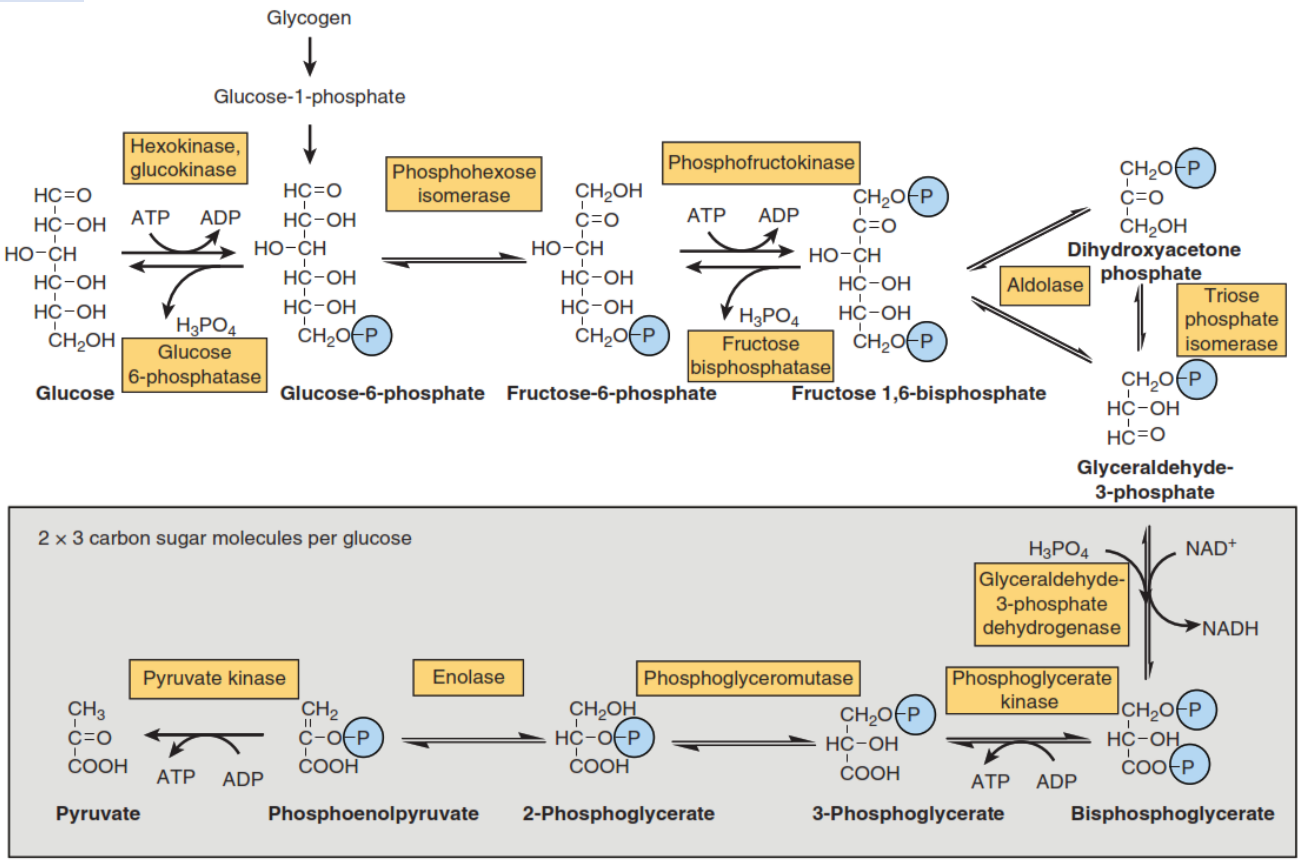
SITE

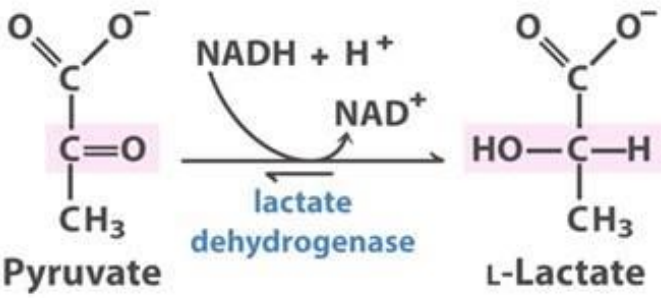
Cytosol of all tissue cells

STAGES OF GLYCOLYSIS

1. **Stage one (the energy requiring stage):**
   - **a)** One molecule of glucose is converted into two molecules of glyceraldehyde-3- phosphates
   - **b)** This step requires **2** molecules of ATP (energy loss)
2. **Stage two (the energy producing stage):**
   - **a)** The **2** molecules of glyceraldehyde-3-phosphate are converted into **pyruvate** (aerobic glycolysis) or **lactate** (anaerobic glycolysis)

STEPS





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BIOLOGICAL IMPORTANCE (FUNCTIONS) OF GLYCOLYSIS

1. **Energy (ATP) production of glycolysis:**

ATP production = ATP produced - ATP utilized.

	ATP produced	*ATP utilized*	*Net*
In absence of oxygen (anaerobic glycolysis)	**4 ATP by (Substrate level phosphorylation)** • **2ATP** from **1,3** BPG. • **2ATP** from phosphoenol pyruvate	**2 ATP** • From glucose to glucose-6-p. • From fructose-6 to fructose1,6 bis p.	**2 ATP**
In presence of oxygen (aerobic glycolysis)	**4 ATP by (Substrate level phosphorylation)** • **2ATP** from **1,3** BPG. • **2ATP** from Phosphoenol pyruvate **6 ATP or 4 ATP** (From oxidation of **2** NADH+H⁺ in mitochondria). See later	**2ATP** • From glucose to glucose-6-p. • From fructose-6- p to fructose 1, 6 bisphosphates.	**6 Or 8 ATP**

2. **Oxygenation of tissues:**
Through formation **2, 3 bisphosphoglycerate**, this **decreases** the affinity of Hemoglobin to O^2.

3. **Provides important intermediates:**
a) Dihydroxyacetone phosphate: may give glycerol-3-phosphate, which is used for **synthesis of triacylglycerols and phospholipids** (lipogenesis).
b) 3-Phosphoglycerate: which may be used for **synthesis of** serine**.**
c) Pyruvate: which may be used in **synthesis of amino acid** alanine**.**

4. **Aerobic glycolysis provides the mitochondria with pyruvate,** which gives **acetyl CoA →** Krebs' cycle.

5. **very important in: (**because the glucose is the most dependent source of energy**)**
   - **Tissues with no mitochondria:** mature RBCs, cornea and lens
   - **Tissues with few mitochondria:** Testes, leucocytes, medulla of the kidney, retina, skin and gastrointestinal tract.
   - **Tissues undergo frequent oxygen lack:** skeletal muscles especially during exercise

6. **Functions of glycolysis in RBC:**
   1. Mature RBCs contain **no mitochondria thus:**
      a) They depend only upon glycolysis for energy production (=2 ATP).
      b) Lactate is always the end product.
   2. Glucose uptake by RBCs is insulin **in**dependent.
   3. **Reduction of met-hemoglobin: Met-hemoglobin** binds oxygen irreversibly. Glycolysis produces NADH+H, which used for reduction of met-hemoglobin in red cells, into hemoglobin. This reaction is catalyzed by "**cytochrome b_5-met-haemoglobin reductase"** system (cyt b5).

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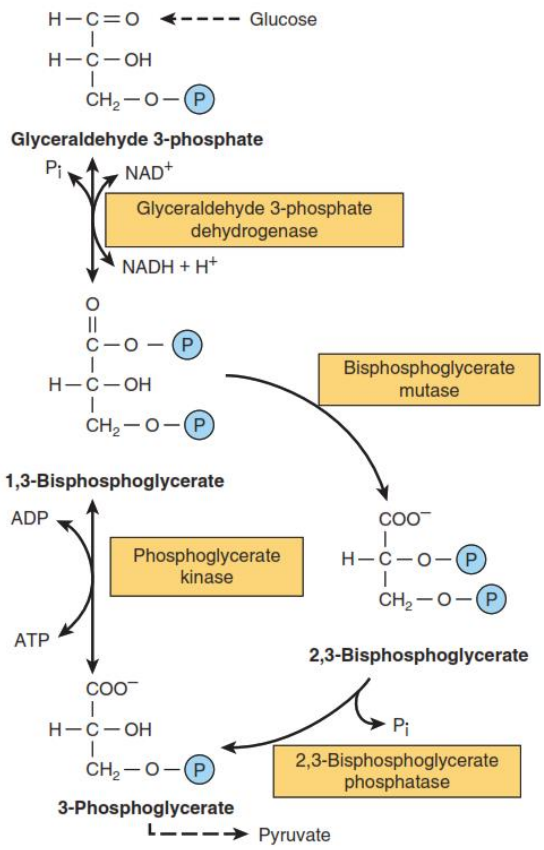
4. **2,3 Bisphosphoglycerate (2,3 BPG):**
   a) The RBCs have the ability to form **2, 3** bisphosphoglycerate **(2, 3** BPG) through what is called: (**Rapoport-Luebering cycle**) or (**2, 3 b**isphosphoglycerate cycle).
   2, 3 BPG ↓ affinity of hemoglobin to **O_2** → Good oxygenation of tissues.
   b) **Mechanism:**
   In the erythrocytes of many mammalian species the reaction



DIFFERENCES BETWEEN AEROBIC AND ANAEROBIC GLYCOLYSIS

	Aerobic	Anaerobic
End product	Pyruvate	Lactate
Energy	**6** or **8** ATP	**2** ATP
Regeneration of NAD	Through respiratory chain in mitochondria	Through lactate formation
Availability to TCA in mitochondria	Available and **2** pyruvate can oxidize to give **30** ATP	Not available as lactate is cytosolic substrate

IMPORTANCE OF LACTATE PRODUCTION IN ANAEROBIC GLYCOLYSIS:

- In absence of oxygen, NADH+H⁺ is not oxidized by the respiratory chain, thus: **The conversion of pyruvate to lactate is the mechanism for regeneration of NAD.**

This helps continuity of glycolysis, as the generated NAD will be used once more for oxidation of another glucose molecule.

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Regulation of glycolysis

The rate of glycolysis is regulated by controlling of the **three irreversible enzymes** (key enzymes). These enzymes catalyze what is called committed reactions of the pathway.

These enzymes are: **Glucokinase (Hexokinase), phosphofructokinase-1** and **pyruvate kinase.**

	Glucokinase	*Hexokinase*
Site	Liver only	All tissue cells
Affinity to glucose	Low affinity (high km) i.e. it acts only in the presence of high Glucose blood concentration.	High affinity (low km) i.e. it acts even in the presence of low blood Glucose concentration.
Substrate	Glucose only	Glucose, galactose and fructose
Effect of insulin	Induces synthesis of Glucokinase	No effect
Effect of glucose-6-phosphate	No effect	Allosterically inhibits Hexokinase
Function	Acts in liver after meals. It removes glucose coming in portal circulation, converting it into glucose-6-phosphate	It phosphorylates glucose inside the body cells. This makes glucose concentration more in blood than inside the cells This leads to continuous supply of glucose for the tissues even in the presence of low blood glucose

- **Hormonal regulation:**
  a) Insulin: **Stimulates** synthesis of all key enzymes of glycolysis. It is secreted after meal (in response to high blood glucose level).
  b) **Glucagon:** **Inhibits** the activity of all key enzymes of glycolysis. It is secreted in response to low blood glucose level.
- **Energy regulation:**
  a) High level of ATP inhibits PFK-1 and pyruvate kinase.
  b) High level of ADP and AMP stimulate PFK-1.

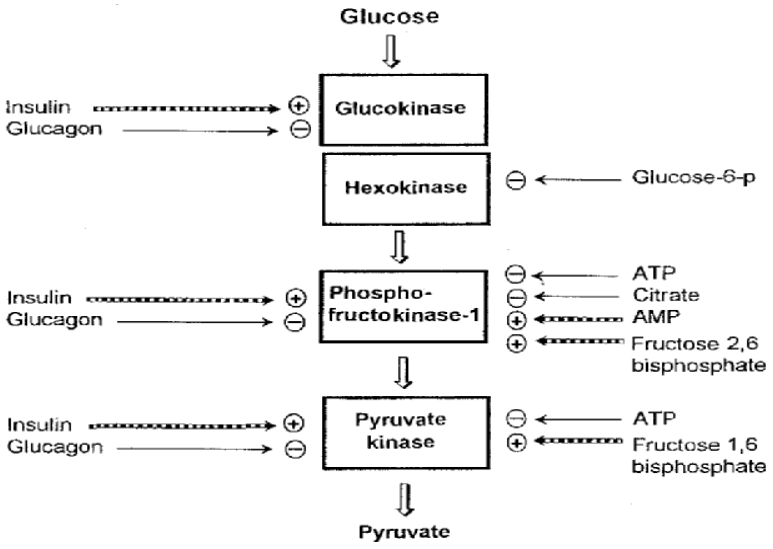
Substrate regulation:

a) Glucose-6-phosphate inhibits Hexokinase (and not Glucokinase).

b) Fructose 2, 6 bisphosphate stimulates PFK-1.

c) Citrate inhibits PFK-1.

d)Fructose 1,6 bisphosphate stimulates pyruvate kinase.



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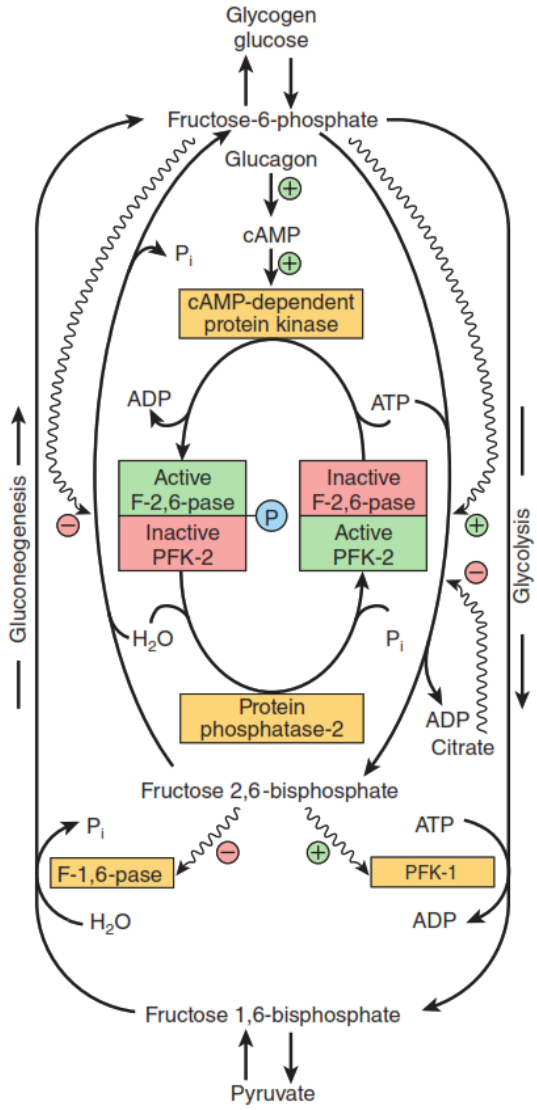
- **Fructose 2, 6 bisphosphate:**
  a) This substrate is produced from **fructose-6-phosphate** by reaction catalyzed by: phosphofructokinase-2 (PFK-2) enzyme.
  b) Fructose 2, 6 bisphosphate stimulates glycolysis by allosteric stimulation of PFK-1. It also inhibits gluconeogenesis by inhibiting fructose 1, 6 bisphosphatase enzyme.



Clinical aspects of glycolysis:

There are many diseases associated with impaired glycolysis they include:

- **Pyruvate kinase (PK) deficiency:**
  a) This leads to excessive **hemolysis** of RBCs → leading to hemolytic anemia.
  b) Genetic deficiency of PK enzyme causes decrease the rate of glycolysis and decrease production of ATP.
  c) ATP is required for Na-K ATPase, which is important for stability of RBCs.

- **Hexokinase deficiency:**
  It leads to hemolytic anemia due to decrease ATP production.
  The mechanism is similar to that of PK deficiency.

- **Lactic acidosis:**
  Definition: It is the lowered blood pH and bicarbonate levels due to increased blood lactate above normal level.
  Mechanism: This depletes bicarbonate → ↓pH of blood → Lactic acidosis may lead to coma.
  Causes: **It** results from increased formation OR decreased utilization of lactate.
  1) Increased formation of lactate: as in severe muscular exercises.
  2) Decreased utilization of lactate in tissues: if occurs in cases of anoxia or lack of oxygen e.g. myocardial infarction, respiratory disorders and anemia.
  3) Phenformin: is oral hypoglycemic drug causing excessive anaerobic oxidation of glucose and excess lactate production.

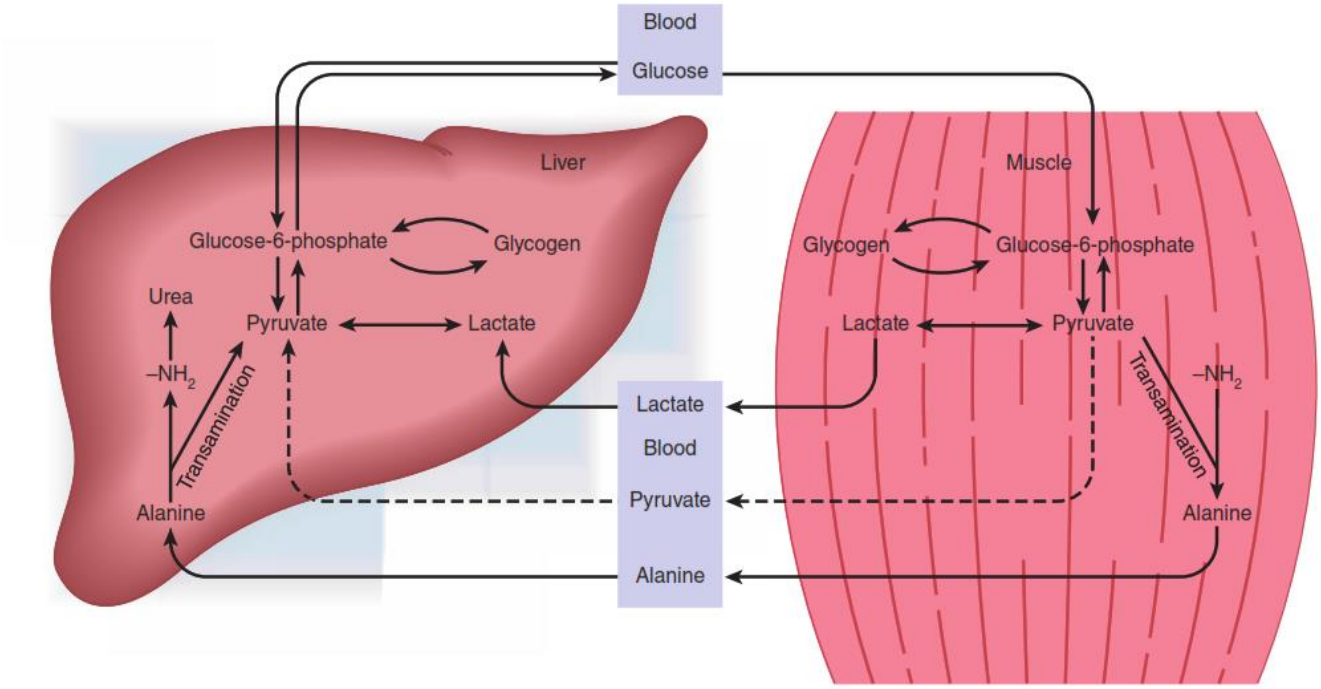
Lactate

a) Sources: From glycolysis especially in RBCs due to absence of mitochondria and Muscle during exercises due to oxygen lack

b) Fate:

1) Glucose formation: [**through lactic acid cycle (Cori cycle)**]:
   - Lactate formed in muscles and RBCs may diffuse to the blood then to the liver.
   - In the liver, lactate is converted to glucose by gluconeogenesis. Glucose may diffuse back to the blood, then to red cells or muscles to be used for production of energy.
2) Conversion into pyruvate: If oxygen gets available, lactate is converted into pyruvate, which proceeds into **Kreps cycle**
3) Lactate may be accumulated in muscles causing muscle fatigue.
4) Lactate is excreted in urine and sweat

Definition of Cori cycle: It is the conversion of glucose into lactate in **peripheral tissues**. Followed by conversion of lactate into glucose in **liver**.



Lactate dehydrogenase

1. It is an enzyme which catalyzes the reaction: **Lactate ↔ Pyruvate**
2. This reaction helps the re-oxidation of NADH+H into NAD.
3. It has 5 isoenzymes: LD1, LD2, LD3, LD4 and LD5.
4. **Medical importance:**

Estimation of the activity of lactate dehydrogenase enzyme in plasma helps the diagnosis of heart and liver diseases:

a) LD1: Elevated in some heart diseases e.g. myocardial infarction.
b) LD5: Elevated in some liver diseases as acute viral hepatitis.

In vitro inhibition of glycolysis

1- Arsenate: by competing with inorganic phosphate in the reaction:

glyceraidhyde-3 -p → 1,3 bisphosphoglycerate

2. Iodoacetate: by inhibiting glyceraldhyde-3-p dehydrogenase.

3. Fluoride: Inhibits enolase enzyme. Clinical laboratories use fluoride to inhibit glycolysis by adding it to the blood before measuring blood glucose.

MITOCHONDRIAL PATHWAY FOR GLUCOSE OXIDATION

- Complete oxidation of glucose occurs in both Cytosol (glycolysis) and mitochondria (Krebs' cycle).
- In the presence of O_2, pyruvate (the end product of glycolysis) passes by special pyruvate transporter into mitochondrion which proceeds as follows:

  Oxidative decarboxylation of pyruvate to Acetyl-COA.

  Acetyl CoA is then oxidized completely to CO_2, H_2O through Krebs' cycle

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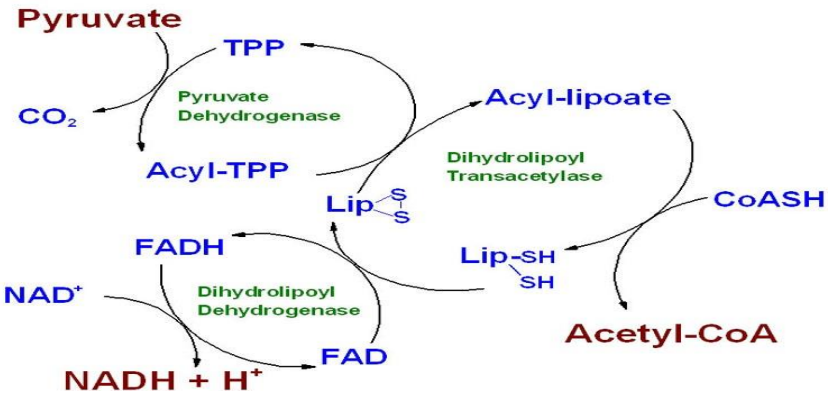
OXIDATIVE DECARBOXYLATION OF PYRUVATE TO ACETYL COENZYME A (= ACETYL COA)

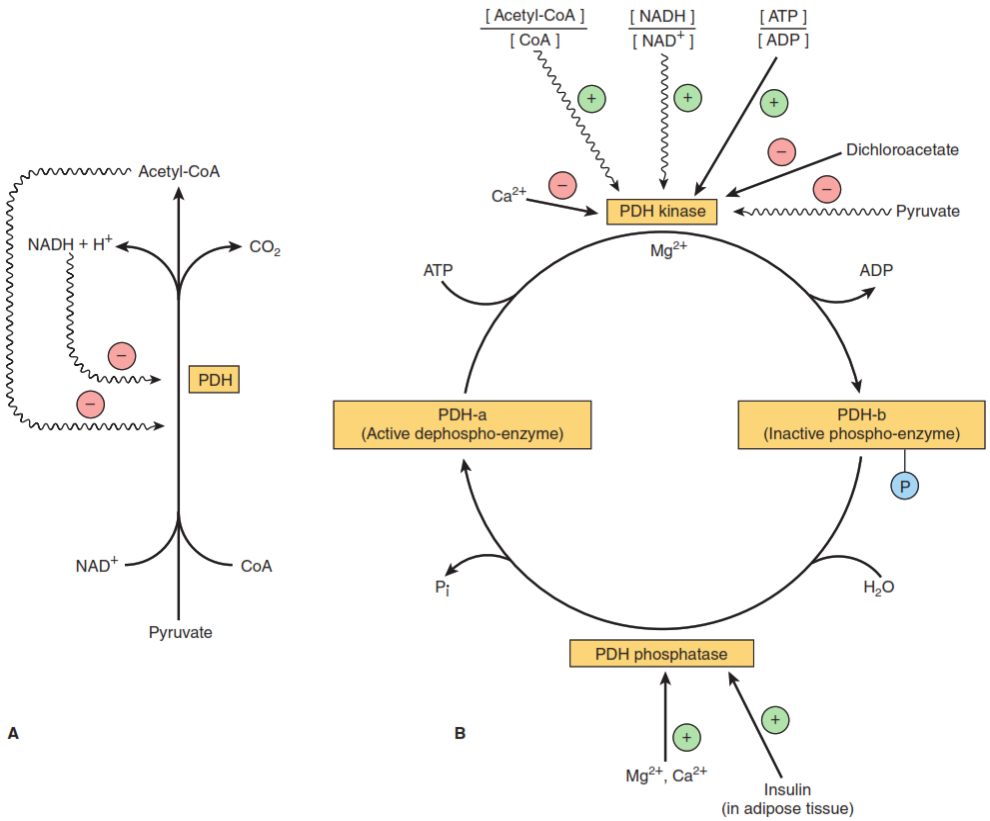
- **Enzyme:** Pyruvate dehydrogenase (PDH) complex:
  - **a) Structure:** contains 3 subunits, which catalyzes the reaction in 4 steps. These subunits are: pyruvate decarboxylase, dihydrolipoyl transacetylase and dihydrolipoyl dehydrogenase.
  - **b) Coenzymes:** needs 5 coenzymes (all are vitamin B complex derivatives):
    1) Vitamin B1 = Thiamin pyrophosphate = TPP.
    2) Lipoic acid
    3) Coenzyme A = CoASH.
    4) Flavin adenine dinucleotide = FAD.
    5) Nicotinamide adenine dinucleotide = NAD+.
  - **c) Location:** PDH is located within the mitochondrial matrix.
- **Reactions:**



- **Energy production:** → **NADH+H** (through respiratory chain) **→3ATP**
- **Regulation of oxidative decarboxylation (PDH):**
  a) PDH exists in two forms: Phosphorylated (inactive) and dephosphorylated (activated).
  - PDH kinase enzyme converts active into inactive PDH enzyme.

  In vitro inhibition of PDH:

  a) Arsenic. b) Thiamin (B1) deficiency



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MCQ

1. **The product of glycolysis in erythrocytes is:**
   a- NADPH b- Lactate c- Pyruvate d- Carbon dioxide
2. **Glucokinase is more active after a meal, because:**
   a- It is an inducible enzyme. b- It has more affinity to glucose than hexokinase
   c- It is present in all tissues d- Can act on all monosaccharides
3. **An example of substrate level phosphorylation is:**
   a- Isocitrate Dehydrogenase b- Enolase
   c- Pyruvate kinase d- Glyceraldehyde-3-phosphate dehydrogenase
4. **Which enzyme catalysis an irreversible reaction?**
   a- Transketolase b- Phospho fructokinase
   c- Aldolase d- Glyceraldehyde-3-phosphate dehydrogenase
5. **Which enzyme in glycolytic pathway is inhibited by fluoride ions?**
   a- Hexokinase b- phosphofructokinase c- Aldolase d- Enolase
6. **During anaerobic glycolysis NAD+ is regenerated from NADH by:**
   a- Glyceraldehyde-3-phosphate dehydrogenase b- Oxygen
   c- Glutamate dehydrogenase d- Lactate dehydrogenase
7. **All the enzymes listed below are regulatory enzymes, EXCEPT:**
   a- Glycogen phosphorylase b- Glucose-6-phosphate dehydrogenase
   c- Pyruvate kinase d- Lactate dehydrogenase
8. **ATP is generated in all the following reactions EXCEPT:**
   a- Glyceraldehyde-3-phosphate dehydrogenase b- I ,3-bisphosphoglycerate kinase
   c- Pyruvate kinase d- Hexokinase
9. **The key enzyme of glycolysis is:**
   a- Glucose-6-phosphatase b- Glyceraldehyde-3-phosphate dehydrogenase
   c- Phosphohexose isomerase d- Phosphofructokinase
10. **Catalytic activity of phosphofructokinase is increased by:**
    a- AMP c- ATP b- Fructose-I ,6-bisphosphate d- Fructose-I -phosphate
11. **Complete Oxidation of one molecule of glucose yields how many ATPs?**
    a- 12 b- 24 c. 38 d. 129
12. **All the following coenzymes are involved in the pyruvate dehydrogenase reaction EXCEPT:**
    a. Thiamine pyrophosphate (TPP) b- Biotin c- NAD^+ d- FAD
13. **There is no net synthesis of glucose from fatty acids, because of the irreversible nature of the reaction:**
    a- Pyruvate to oxaloacetate b- Pyruvate to acetyl COA
    c- Phosphoenol pyruvate to pyruvate d- Oxaloacetate to Phosphoenol pyruvate
14. **Pyruvate is converted to acetyl COA by:**
    a- Pyruvate dehydrogenase b- Pyruvate carboxylase
    c- Pyruvate kinase d- Lactate dehydrogenase
15. **In glycolysis, the following reactions are irreversible, EXCEPT that catalyzed by:**
    a- Glucokinase. b- Phosphoglycerate kinase. c- PFK-1 d- Pyruvate kinase.
16. **Phosphoglycerate kinase catalyzes conversion of BPG into:**
    a-2,3 BPG. b- 2-phosphoglycerate. c- 3-phosphoglycerate. d- Non of the above.

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KREBS' CYCLE

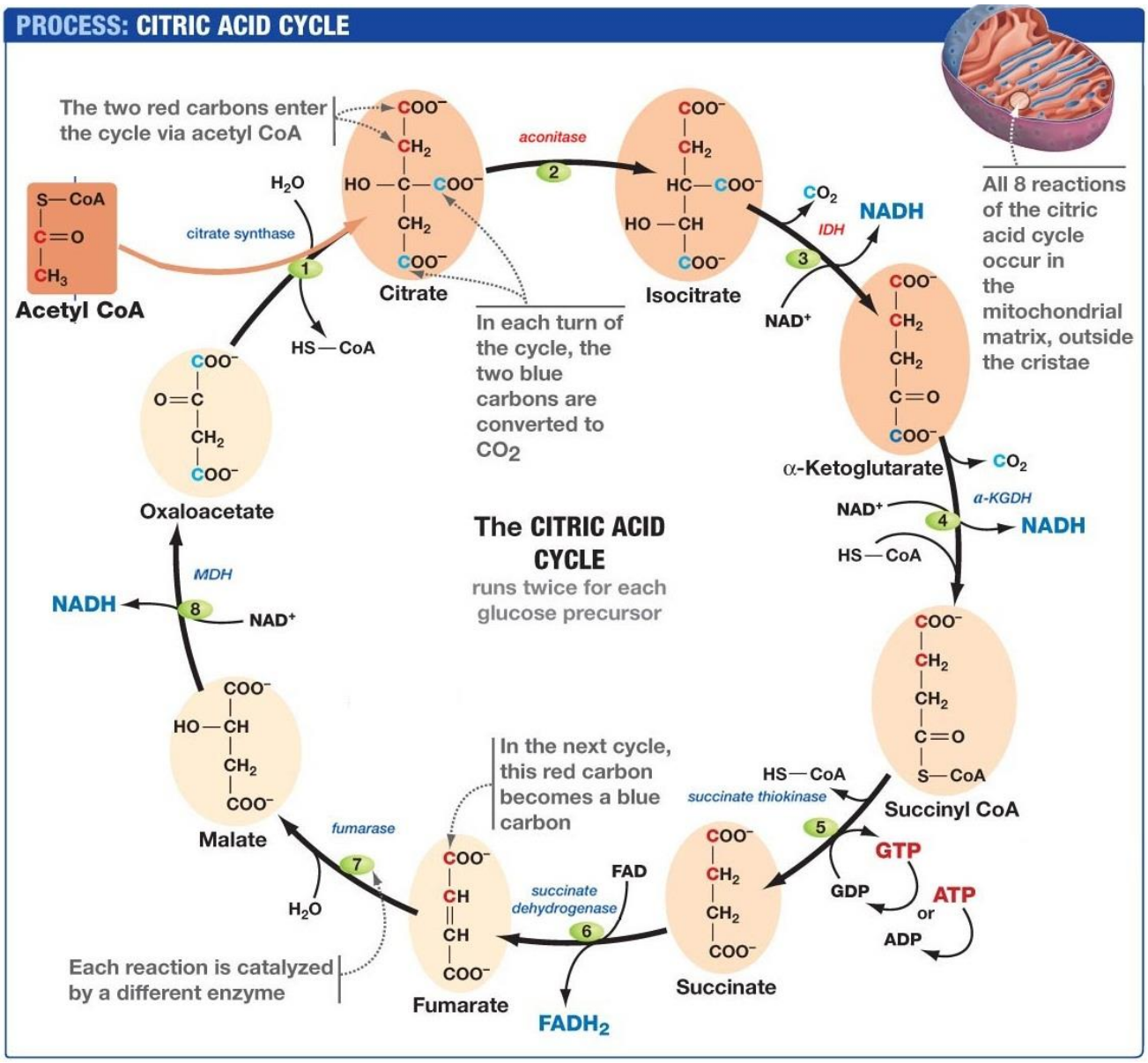
Citric acid cycle (CAC), tricarboxylic acid cycle (TCA) or Catabolism of acetyl CoA

DEFINITION series of reactions in which acetyl CoA is oxidized into CO2, H2O and energy.

LOCATION Mitochondria

STEPS

Citrate Is Krebs' Starting Substrate For Making Oxaloacetate.



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ENERGY PRODUCTION OF TCA:

Enzyme	*Method of ATP production*	*No. of ATP*
Isocitrate dehydrogenase	Oxidation of $NADH+H^+$ by respiratory chain	**3 ATP**
α-Ketoglutarate DH	Oxidation of $NADH+ H^+$ by respiratory chain	**3 ATP**
Succinyl CoA thiokinase	Substrate level phosphorylation	**1 ATP**
Succinate dehydrogenase	Oxidation of $FADH_2$ by respiratory chain	**2 ATP**
Malate dehydrogenase	Oxidation of $NADH+H^+$ by respiratory chain	**3 ATP**
Total =		**12 ATP**

FUNCTIONS (SIGNIFICANCE) OF TCA: TCA CYCLE IS AMPHIBOLIC

I.e. it has catabolic (breakdown) and anabolic (formation) functions.

- **Energy:** 12 ATP
- **Catabolic functions:** Oxidation of carbohydrate, lipids and proteins.
- **Anabolic functions:** Formation of:
  - ✓ **Amino acids:** α-Ketoglutarate —Transamination→ Glutamate.
  - ✓ **Glucose:** α-Ketoglutarate —Gluconeogenesis→ Glucose.
  - ✓ **Heme synthesis:** Succinyl CoA → Heme.
  - ✓ **Fatty acid and cholesterol.**
  - ✓ **CO_2:** is used in the (CO_2 fixation reactions) (carboxylation reactions) :
- **Requirements:** 1- Enzyme: carboxylase. 2- Co-enzyme: Biotine
  3- CO_2 4- ATP
- **Important Reactions:**
- **CHO:** Pyruvate + CO_2 → Oxaloacetate —Gluconeogenesis→ Glucose
- **Lipid:** Acetyl COA + CO_2 → Malonyl CoA → Fatty acids.
- **Ptn:** Ammonia + ATP + CO_2 → Carbamoyl phosphate → Urea and pyrimidines.
- Propionyl CoA + CO_2 → Methyl malonyl CoA → Succinyl CoA → Intermediate of citric acid cycle.
- Formation of C6 of purines.

IN VITRO INHIBITION OF TCA CYCLE:

a) Fluoroacetate (F_1- CH_2-COSCoA): inhibits **aconitase** enzyme.
b) Arsenate: inhibits α-Ketoglutarate dehydrogenase enzyme.
c) Malonic acid: inhibits Succinate dehydrogenase enzyme (competitive inhibition.

REGULATION OF CITRIC ACID CYCLE

TCA is regulated through the key enzymes (citrate synthase, Isocitrate DH and α-Ketoglutarate DH) and the availability of **CO_2**

a) Citrate synthase

1) Stimulated by: acetyl CoA, oxaloacetate, ADP and NAD.
2) Inhibited by: long chain acyl CoA, citrate, Succinyl CoA, ATP and $NADH+H^+$

b) Isocitrate dehydrogenase and α-Ketoglutarate dehydrogenase:

1) Stimulated by: NAD, ADP.
2) Inhibited by: $NADH+H^+$ and ATP.

c) Availability of Oxygen: Citric acid cycle needs oxygen to proceed. This is because in absence of oxygen, respiratory chain is inhibited leading to increase **$NADH+H^+$** → inhibition of TCA cycle.

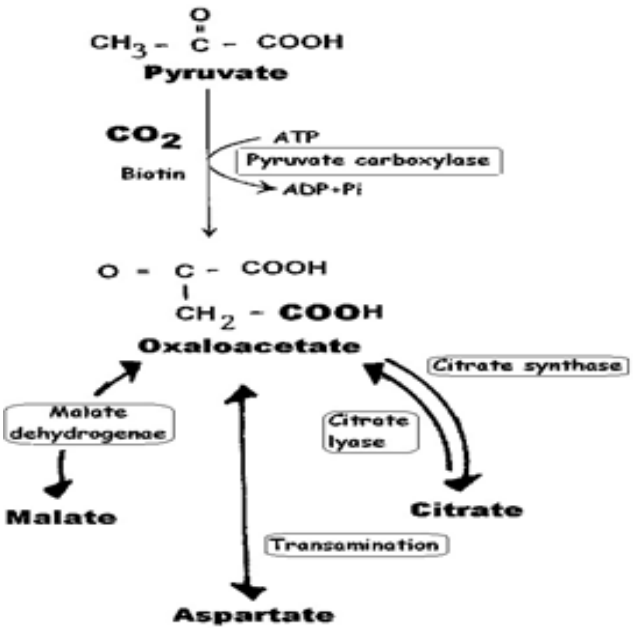
SOURCES AND FATE OF OXALOACETATE

a) Sources of oxaloacetate:

1) **Oxidation of Malate.**
2) **Transamination of Aspartate:**
3) **Carboxylation of pyruvate**
4) **Cleavage of citrate**

b) Fate of oxaloacetate:

1) **Formation of citrate:**
2) **Reduction to Malate.**
3) **Transamination into aspartate**



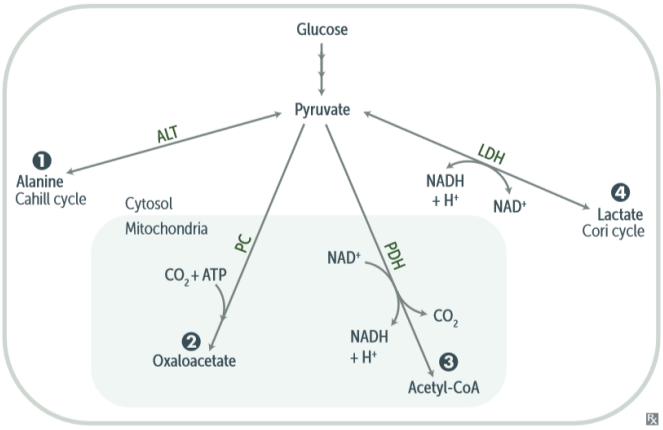
SOURCES AND FATE OF PYRUVATE

Sources

1. **Glucose:** glycolysis.
2. **Lactate:** by lactate DH
3. **Malate:** by malic enzyme.
4. **Alanine:** by transamination.
5. **Serine:** by non-oxidative deamination.
6. **Other amino acids:** methionine

Fate

1. **Glucose formation:** gluconeogenesis.
2. **Lactate formation:** by lactate DH.
3. **Malate formation:** by malic enzyme.
4. **Alanine formation:** by transamination.
5. **Oxaloacetate formation:** by pyruvate carboxylase.



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MCQ

17. How many ATPs are generated per one rotation of the citric acid cycle?

a- 2 b- 8 c- 12 d- 15

18. The following reaction produces ATP at the substrate level:

a- PFK-1 b. Aldolase. c. Phosphoglycerate kinase. d- Glycaaldehyde-3P dehydrogenase.

19. Oxidation of glucose in RBCs gives:

a- 2ATP. b- 3 ATP. c- 8 ATP. d. None of the

20. PFK-1 is inhibited by all. EXCEPT:

a- ATP b- Citrate. c. Glucagon. d- AMP

21. Conversion of glucose phosphate to fructose-1,6 bisphosphate requires:

a- Phosphoglucomutases and phosphorylase. b-Phosphoglucomutases and aldolase.
c. Phosphohexose and phosphofructokinase
d. Phosphoglucomutases and phosphofructokinase- 1

22. Pyruvate can be converted to :

a- Lactate b- Nanine c- Oxaloacetate. d. All of the above.

23. Pyruvate dehydrogenase complex, requires all,

a- NAD. b- COA. C- ATP d- Pyruvate.

24. All the following correctly pairs coenzyme with its enzyme, EXCEPT:

a- Succinate dehydrogenase, FAD. b- Malate dehydrogenase NAD.
c- Acetyl COA carboxylase, biotin. d- Pyruvate dehydrogenase PLP.

25. Oxidative decarboxylation of a-ketoglutarate requires an, EXCEPT:

a- FAD b- COASH. c. PLP. d- Lipoate

26. In TCA cycle the only enzyme which requires FAD is:

a- Iso-citrate dehydrogenase. b- a-ketoglutarate dehydrogenase.
c- Succinate dehydrogenase. d- Malate dehydrogenase.

27. All of the following are Krebs' cycle intermediates, EXCEPT:

a- Acetoacetate. b- Cis aconitate. c. Succinate d- Fumarate.

28. The release or carbon dioxide results from the following reaction of the citric acid cycle:

a- Citrate to isocitrate. b-Fumarate to malate.
c- Malate to oxaloacetate. d- Isocitrate to a-ketoglutarate.

29. In pyruvate kinase (PK) deficiency, hemolysis of red cells occurs primarily because of increased intracellular levels of:

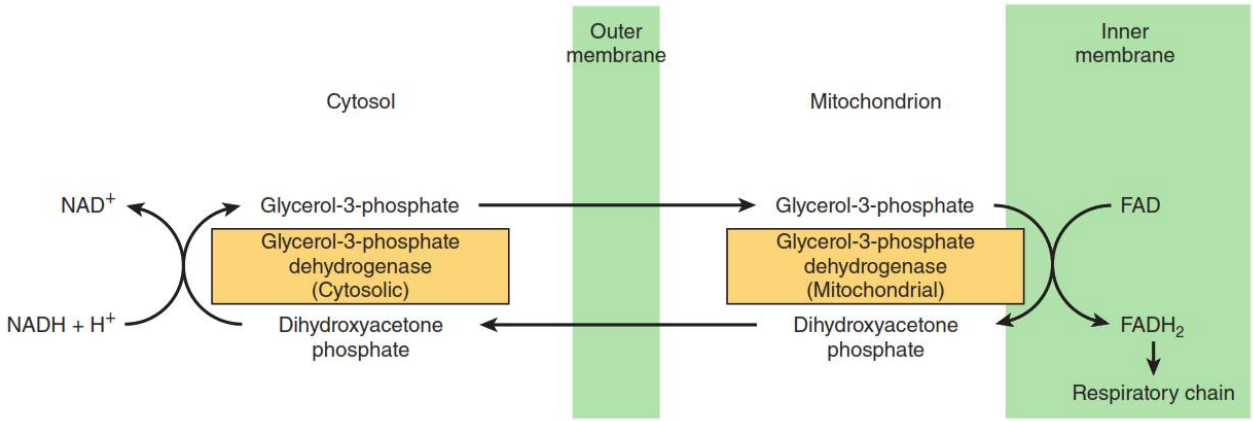
a- Lactate. b- Pyruvate.
c- ADP to ATP ratio. d- 2,3-diphosphoglycerate.

OXIDATION OF EXTRA MITOCHONDRIAL NADH+H$^+$

1. The molecules of cytosolic NADH+H$^+$ cannot penetrate mitochondrial membrane; however, they can be used to produce energy by respiratory chain phosphorylation in the mitochondria.
2. This can be done by using special carriers for hydrogen of NADH+H$^+$ these carriers are either (Glycerophosphate shuttle) or (Aspartate - Malate shuttle).

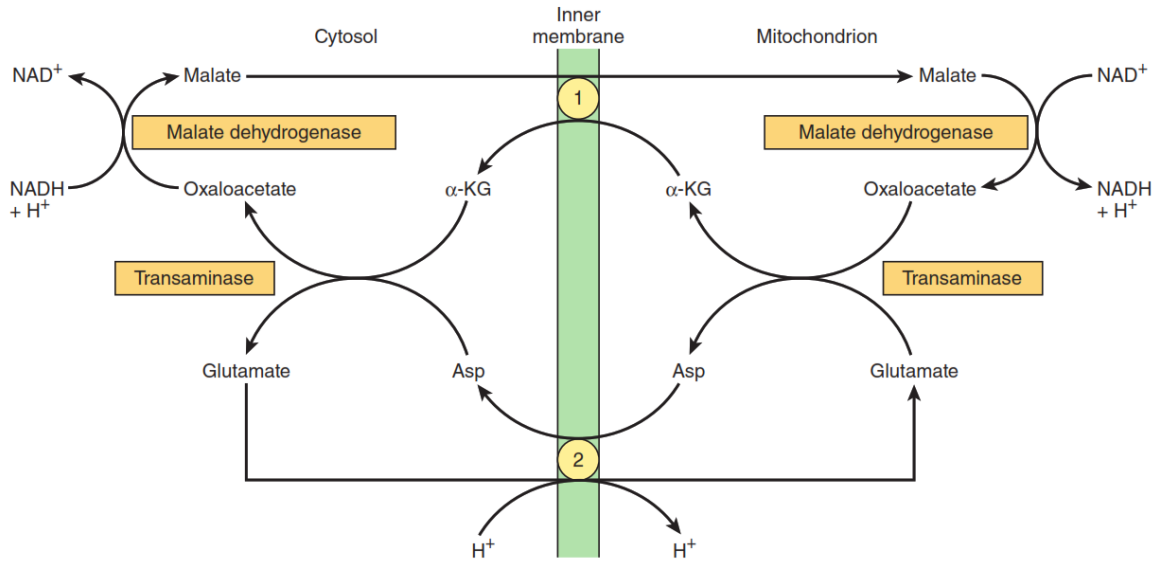
GLYCEROPHOSPHATE SHUTTLE

- It is important in certain muscles and nerve cells.
- The final energy produced is **2** x **2** ATP → **4** ATP.
- **Mechanism:**
  - The coenzyme of cytosolic (glycerol -3- phosphate DH) is NAD$^+$.
  - The coenzyme of mitochondrial (glycerol -3- phosphate DH) is FAD.



MALATE - ASPARTATE SHUTTLE

- It is important in tissues particularly liver and heart.
- The final energy produced is **2 x 3** ATP → **6** ATP
- Mechanism**:**
  - The coenzyme of cytosolic and mitochondrial (Malate dehydrogenase) is NAD$^+$



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RESPIRATORY CHAIN
(ELECTRON TRANSPORT CHAIN)

DEFINITION

It is the final common pathway in aerobic cells by which electrons derived from various substances are transferred to oxygen to form water.

SITE

Mitochondria in all over body cells except: (RBC, cornea).

ORGANIZATION OF THE RESPIRATORY CHAIN

- The inner mitochondrial membrane contains 5 **fixed enzyme complexes**, called complex I, II, Ill, IV and V. **Complex V catalyses ATP synthesis**.

a) Each complex accepts or donates electrons to relatively 2 **mobile electron carriers** such as **coenzyme Q** and **cytochrome C**.

b) Each carrier of electron transport chain can receive electrons from the more electronegative donor to the next more electropositive carrier in the chain.

- Finally electrons combine with **oxygen** and protons to form water.

COMPONENT

a) Complex I: Contains an enzyme called (NADH dehydrogenase)
   (i) Its coenzyme is FMN.
   (ii) It contains several iron and sulfur atoms.
   (iii) It oxidizes NADH+H into NAD. And converts its coenzyme FMN into $FMNH^2$.

b) Complex II: Contains an enzyme called: (flavoprotein dehydrogenase) e.g. Succinate dehydrogenase of TCA **and** acyl COA dehydrogenase of fatty acid oxidation.
   (i) Its coenzyme is FAD.
   (ii) It contains iron and sulfur atoms.

c) Complex Ill: contains an enzyme cytochrome b.

d) Complex IV: contains cytochromes a + a3

e) Complex V: catalysis ATP synthesis

REACTIONS OF RESPIRATORY CHAIN

1. Entry via NADH + H^+: NADH + H^+ obtained from reactions catalyzed by dehydrogenase enzymes e.g. dehydrogenase of TCA can join the chain giving electrons to FMN of complex I to coenzyme Q, to cytochrome b, cytochrome c to cytochrome a + a3 to the final acceptor O_2.

2. Entry via $FADH_2$: $FADH_2$ obtained from reactions catalyzed by flavoprotein dehydrogenase e.g. Succinate dehydrogenase can join the chain directly giving electrons to coenzyme Q, then to cytochrome b, c, a + a3 to the final acceptor O_2.

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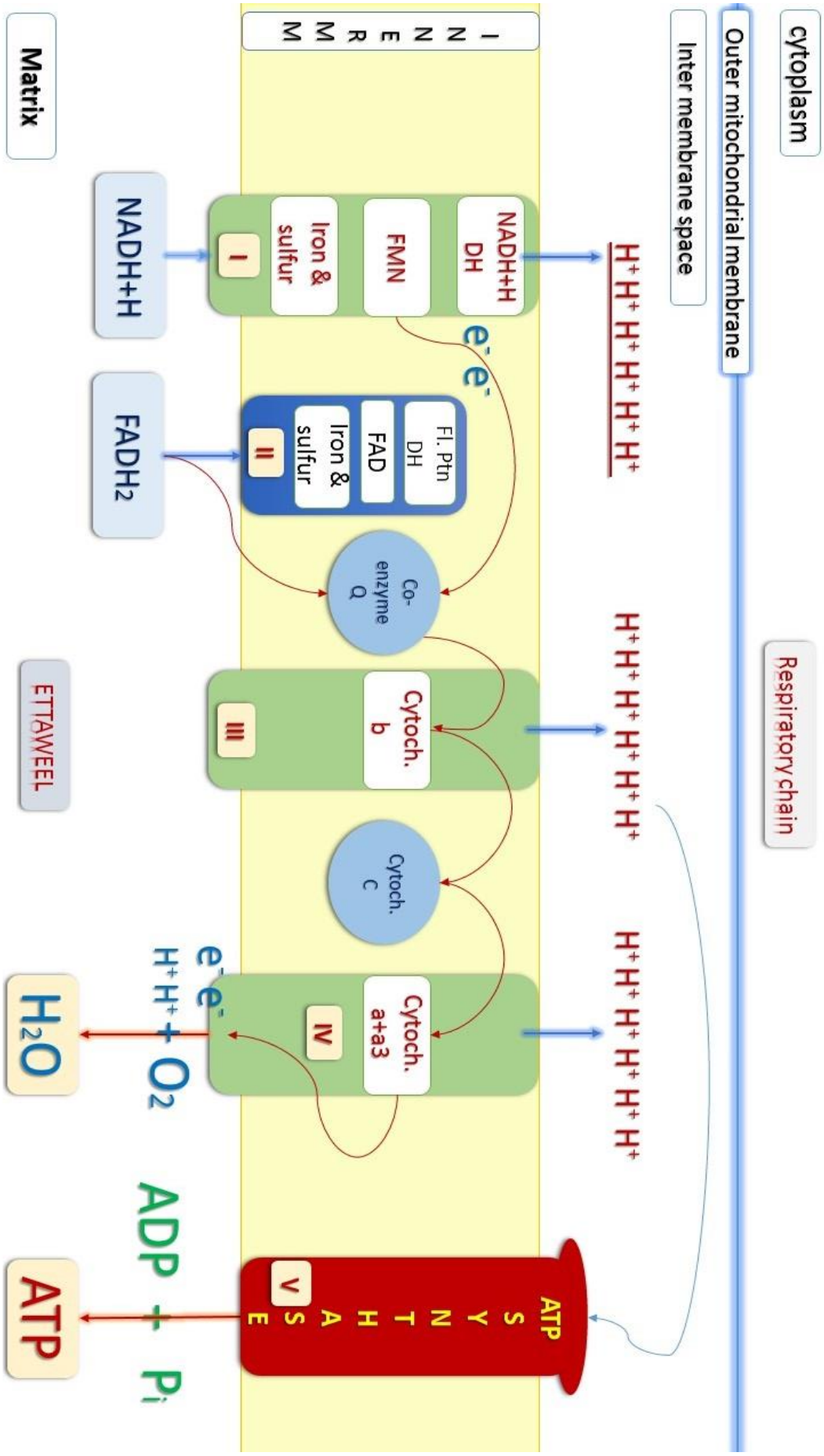
STEPS



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OXIDATIVE PHOSPHORYLATION

A. Introduction:

1. Electrons are transferred down the respiratory chain from NADH to oxygen. This is because **NADH** is a strong electron donor, while **oxygen** is a strong electron acceptor.
2. The flow of electrons from NADH to oxygen (oxidation) results in ATP synthesis by phosphorylation of ADP by inorganic phosphate "Pi" (phosphorylation). Therefore, there is a coupling between oxidation and phosphorylation.

Two theories explain the ATP synthesis, (chemiosmotic hypothesis) and (membrane transport system).

B. Chemiosmotic hypothesis: (Mitchell hypothesis).

- This hypothesis is one form of oxidative phosphorylation. It can be summarized as follows:

1. Proton pump:

a. The transport of electrons down the respiratory chain → Gives energy.

b. This energy is used to transport H+ from the mitochondrial matrix → across inner mitochondrial membrane → inter membrane space.

c. This is done by complexes I, lll and IV.

d. This process creates across the inner mitochondrial membrane:

- **i. An electrical gradient:** (with more positive charges on the outside of the Membrane than on the inside)
- **ii. A pH gradient:** (the outside of the membrane is at lower pH than the inside).

e. The energy generated by Hits proton gradient is sufficient for ATP synthesis.

2. ATP synthase (complex V):

In the inner mitochondrial membrane, there is a phosphorylating enzyme complex: **ATP synthase (or complex V).**

a) It is formed of 2 subunits:

(I) F_1 subunit which protrude into matrix.

(ii) F_o subunit which present in the membrane.

b) The protons outside the inner mitochondrial membrane can re-enter the mitochondrial matrix by passing through channel (F_o - F1 complex) to pass by ATP synthase enzyme which is present in F_1 subunit. This results in the synthesis of ATP from ADP + Pi. At the same time decrease the pH and electrical gradients.

❖ **Evidences support chemiosmotic theory:**

a) Addition of protons (acid) to the external medium of intact mitochondria leads to the generation of ATP.

b) ATP synthesis does not occur in soluble Cytosol system where there is no ATP synthase. A closed membrane as mitochondria must be present in order to obtain oxidative phosphorylation.

C) The component of respiratory chain is organized in a sided manner as required by chemiosmotic theory.

❖ **P/O ratio:** It is the ratio **between** numbers of ADP mole changed into ATP **to** the number of oxygen atom (1/2 O_2) utilized by respiratory chain.

- It is **3:1** if electrons enter through **NAD-coenzyme Q** .
- And it is **2:1** if electrons join the chain **directly** at the level of coenzyme Q.

INHIBITORS OF RESPIRATORY CHAIN

- **Definition:** Are compounds preventing the passage of electrons by binding to a component of the chain, blocking the oxidation, reduction reaction.

Complexes	*Inhibited by*
Complex I (site 1)	Barbiturates, "piericidin A" antibiotic and by the insecticide and fish poison "rotenone"
Complex II	Carboxin
Complex III (site 2)	Antimycin A and dimercaprol.
Complex IV (site 3)	H2S, cyanide (CN-), carbon monoxide and sodium azide.
Complex V	Oligomycin

UNCOUPLERS OF RESPIRATORY CHAIN

- **Definition:** These are substances that **allow** oxidation to proceed but **prevent** phosphorylation. So energy released by electron transport will be lost in the form of **heat**. This explains the cause of hotness after intake of these substances.

Uncoupler	*Mechanism*
Thermogenin Thyroxin	In brown adipose tissues
Oligomycin	Binds to the stalk of the ATP synthase. Closes the H+ channel, and prevent re-entry of protons to the mitochondrial matrix.
2,4 dinitrophenol	It increases the permeability of the inner mitochondrial membrane to proton causing decrease proton gradient.
Calcium and high doses of aspirin:	This explains the fever that accompanies toxic overdoses of these drugs.
Ionophores : e.g. antibiotic "valinomycin"	They have the ability to make a complex with cations as "K+" and facilitate their transport into mitochondria and other biological membranes. They inhibit phosphorylation because they decrease both electrical and pH gradient.

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PENTOSE PHOSPHATE PATHWAY

DEFINITION

It is an alternative pathway for glucose oxidation **where:**

1. ATP (energy) is **neither** produced **nor** utilized.
2. Its main function is to produce **NADPH+H$^+$** and **pentoses**.

LOCATION

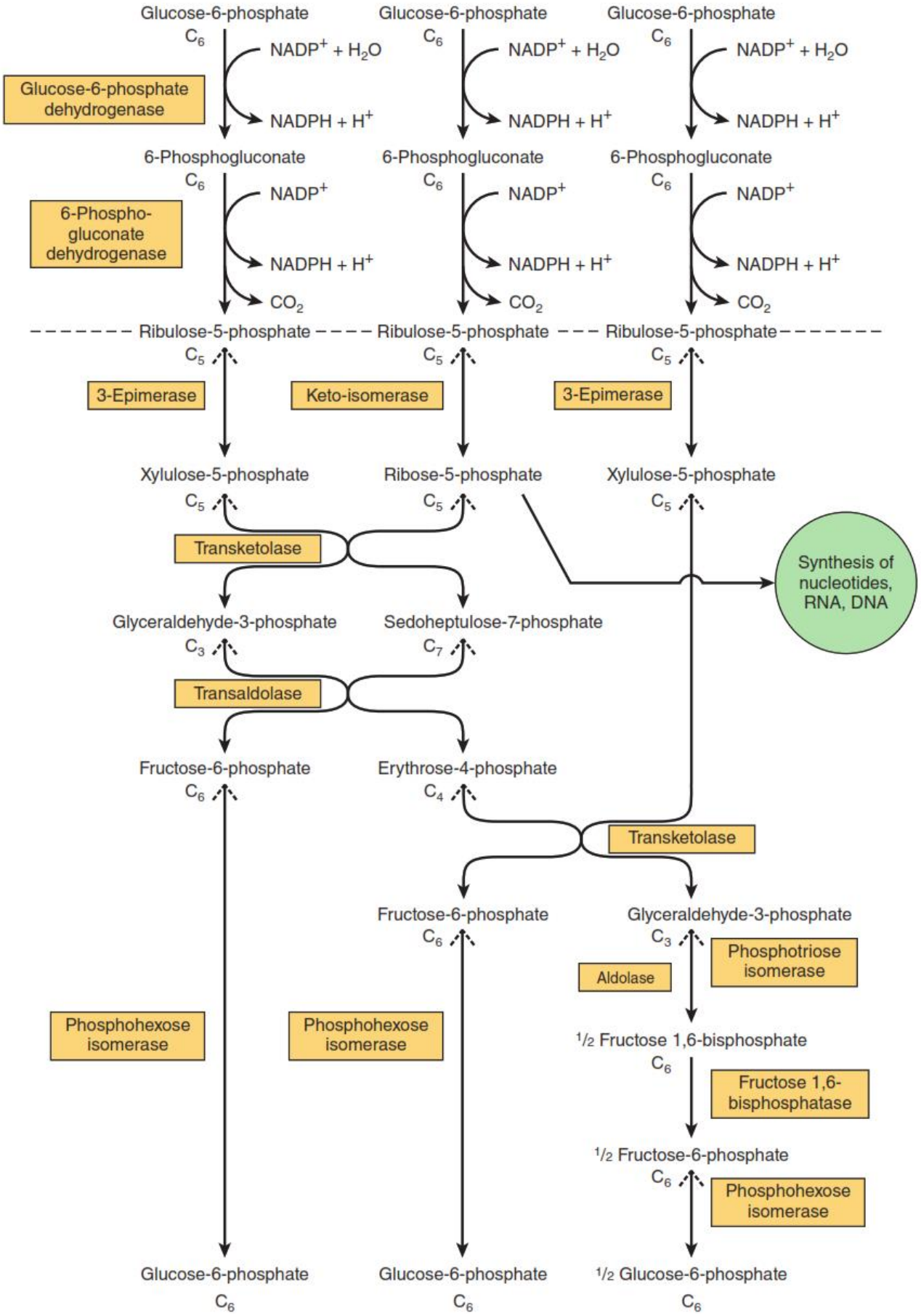
1. **Intracellular location:** Cytosol.
2. **Organ location:**
   a) **It is active in tissues where NADPH+H$^+$ is needed for fatty acids synthesis.**
      1- **Adipose tissue and liver.** 2- **Adrenal cortex and gonads.**
      3- **Red cells** 4- **Retina**
   b) **In many tissues:** It supplies **pentoses** for synthesis of nucleotides.

FUNCTIONS OF HMP PATHWAY

1. **Production of pentoses:**
   Which are essential for synthesis of nucleic acids (RNA and DNA), nucleotides as (ATP, GTP) and coenzymes as (NAD, NADP, FAD).
2. **Production of NADPH+H+:**
   A. **Sources :**
      1. **Pentose phosphate pathway.**
      2. **Malic enzyme** (Malate ⟶ pyruvate).
      3. **Isocitrate dehydrogenase** (cytoplasmic).
   B. **Fate:**
      1- Reductive biosynthesis.
         a) CHO: uronic acid
         b) Lipids: (Fatty acids, cholesterol, steroids, Bile salts).
         c) Proteins: non-essential amino acids.
      2- Reduction of Glutathione.
      3- Reduction of retinal. 4- Reduction of Cyt P450
      5- N.O synthesis 6- sphingosine & galactolipids.
      7- Non-essential amino acid 8- Phagocytosis
      - **Phagocytosis by white blood cells (respiratory burst):**
      Def: It is the rapid consumption of molecular oxygen that accompanies the formation of superoxide by **NADPH oxidase**.
      - Superoxide is then converted into H_2O_2 by **superoxide dismutase** enzyme.
      - **H_2O_2** by **myeloperoxidase** enzyme in the presence of **HCL** is converted into hypochlorite ($HOCL^-$), which kills bacteria.

REACTIONS (STEPS)

- two phases: **oxidative** and **non-oxidative**:
  1. **Oxidative (irreversible) phase:**
     Where **3** molecules of "**glucose-6-phosphate**" are converted into **3** molecules of "**Ribulsose-5-phosphate**" with production of **NADPH+H$^+$** and **CO2**.
  2. **Non-oxidative (reversible) phase:**
     Where the **3** molecules of "**ribulose-5-phosphate**" are interacted and converted into **2** molecules of "**glucose-6-phosphate**" and one molecule of "**glyc-3-phosphate**".



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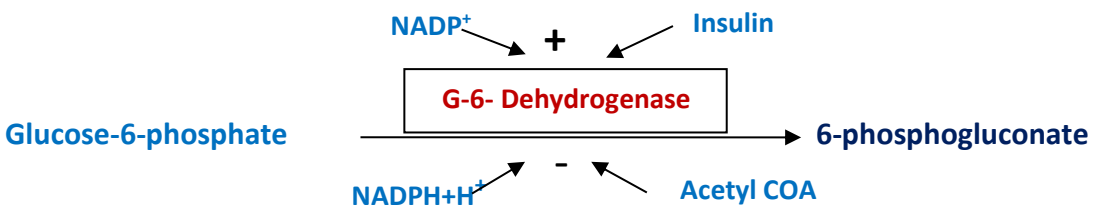
PENTOSE PHOSPHATE PATHWAY IN SKELETAL MUSCLES

- Skeletal muscles obtain their pentose requirement by reversible reactions of pentose phosphate pathway, using **fructose-6-phosphate** and **glyceraldehyde-3-p** and the enzymes transketolase and transaldolase. As they are poor in **G-6-PDH.**

DIFFERENCES BETWEEN HMP SHUNT AND GLYCOLYSIS

	HMP pathway	Glycolysis
Location	In certain cells	In all cells
Oxidation of glucose	Oxidation occurs in the first reaction.	Phosphorylation occurs first then oxidation.
Coenzyme	NADP	NAD^+
Energy	No energy production	2 or 8 ATP
CO2	Produced	Not produced
Pentoses	Produced	Not produced

REGULATION



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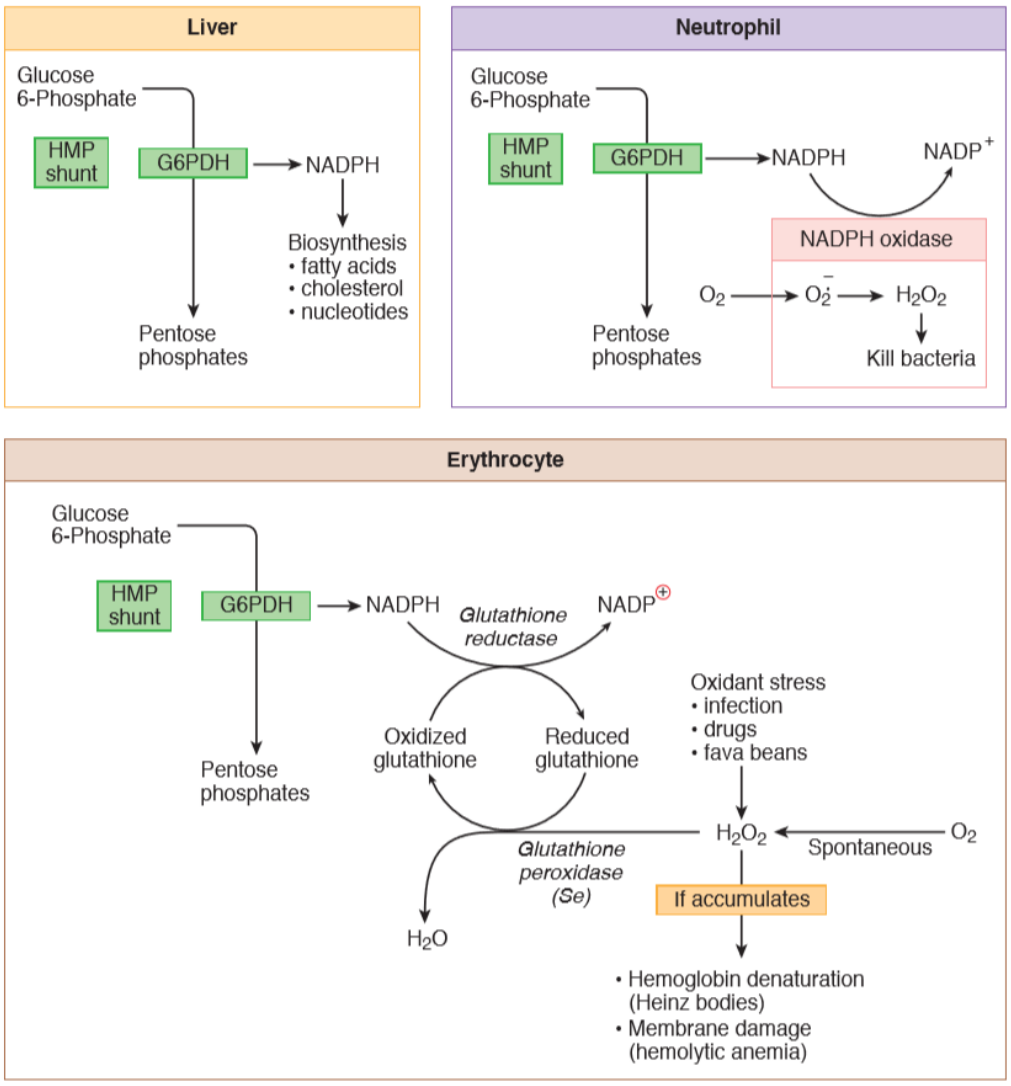
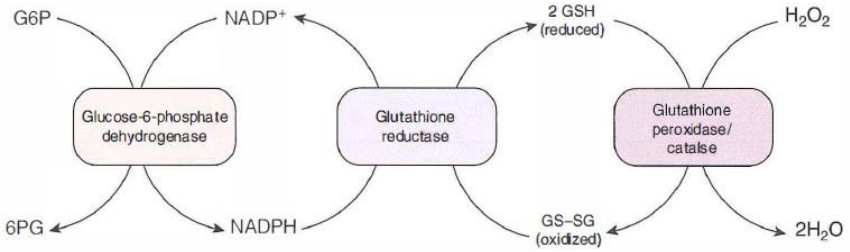


DEFECT OF PENTOSE PHOSPHATE PATHWAY: "FAVISM"

- **Definition:**
  It is type of a **hemolytic anemia** (excessive destruction of RBCs) results after ingestion of **fava beans** and some other compounds (sulfonamide, primaquine, anti-tuberculosis).
- **Cause:** Deficiency of glncose-6-phosphate dehydrogenase enzyme.
- **CCC:** "Heinz bodies"- oxidized Hemoglobin precipitated within RBCs.
- **Mechanism:**
  a) Deficiency of glucose-6-P dehydrogenase 4 Decreased NADPH+H+ production (which is essential to reduce glutathione in RBCs)
  b) Reduced glutathione (G-SH) is needed to remove hydrogen peroxide (H202) which is toxic to the cell.

SIGNS AND SYMPTOMS OF FAVISM

Hemolytic anemia in the form of severe jaundice and decreased hemoglobin.



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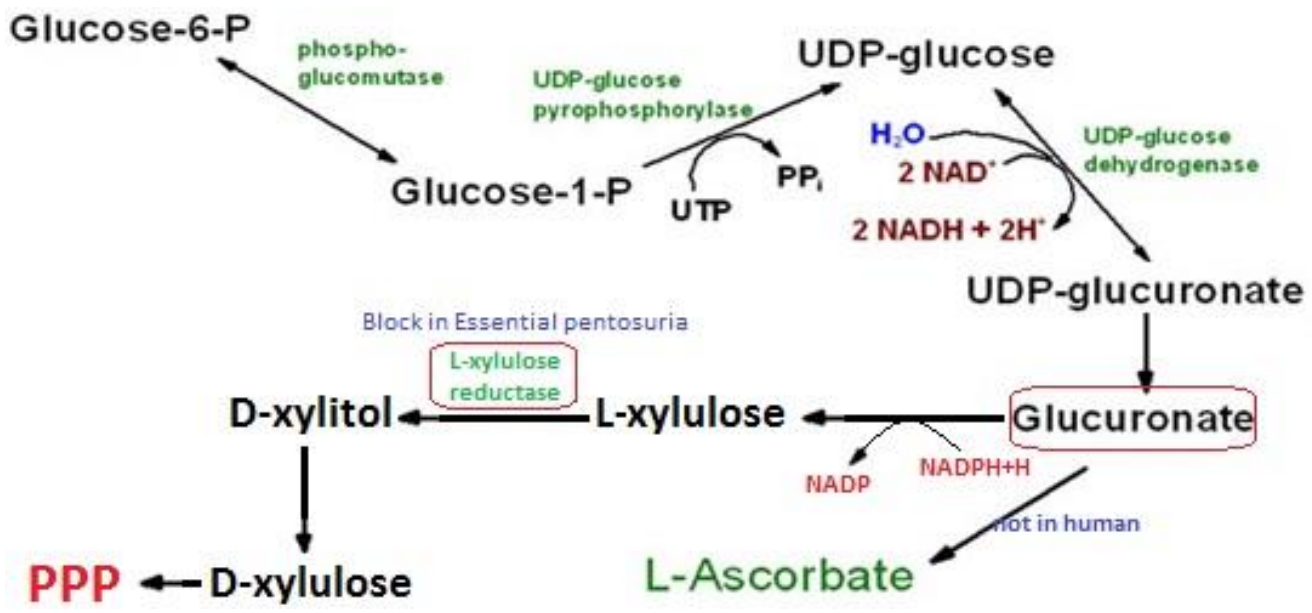
URONIC ACID PATHWAY

Definition It is a minor pathway, in which glucose is converted into glucuronic acid.

LOCATION OF THE PATHWAY:

- **Intracellular location:** Cytosol.
- **Organ location:** Mainly liver.

STEPS



FUNCTIONS (IMPORTANCE) OF URONIC ACID PATHWAY

This pathway produces glucuronic acid, which is important for:

A. Synthesis of substrates:

1. Glycosaminoglycans.

B. Conjugation reactions:

UPD-glucuronic acid is used for conjugation with many body compounds to make them more soluble before excretion e.g. steroid hormones and bilirubin.

C. Detoxification reactions:

UDP-glucuronic acid is used for conjugation with toxic compounds to make them less toxic e.g. phenols.

FATE OF GLUCURONIC ACID:

UDP-glucuronate is converted to glucuronate then → L-xylulose —> D-xylitol → D-xylulose → which then joins **pentose phosphate pathway** to be completely oxidized.

DEFECTS OF URONIC ACID PATHWAY = ESSENTIAL PENTOSURIA:

1. **Definition:** It is benign rare hereditary disease
2. **Cause:** failure of conversion of L-xylulose into D-xylulose (due to deficiency of **L-xylulose reductase**)
3. **Manifestation:** L-xylulose will accumulate and excreted in urine.

Give +ve Bendict test.

MCQ

30. All the dehydrogenases listed below are NAD^+ dependent, EXCEPT:

a. Lactate dehydrogenase
b- Glucose-6-phosphate dehydrogenase
c- Pyruvate dehydrogenase
d- Glyceraldehyde-3-phosphate dehydrogenase

31. The following statements on glucuronic acid pathway are true EXCEPT:

a- It can be synthesized in the human body from active glucose.
b- It can be used in the synthesis of L- ascorbic acid in human body.
c- It is used in detoxication of benzoate.
d- It conjugates with bilirubin in the liver.

32. Which enzyme generates NADPH?

a- Pyruvate carboxylase
b- Pyruvate dehydrogenase
c- Glucose-6-phosphate dehydrogenase
d- Lactate dehydrogenase

33. Transketolase activity is decreased in the deficiency of:

a- Thiamine pyrophosphate (TPP)
b- Nicotinamide adenine dinucleotide
c- Flavin adenine dinucleotide
d- Pyridoxal phosphate

34. The HMP shunt pathway is important for all the following

a- Generation Of ATP
b- Fatty acid biosynthesis
c- Synthesis of reduced glutathione
d- Synthesis of ribose

35. HMP pathway occurs in the cytosol of:

a- Liver.
b- Adipose tissue.
c- Testis.
d- All of the above.

36. NADPH is important FOR ALL Except:

a- Fatty acid synthesis.
b-Hydroxylation reactions.
c- Gluconeogenesis.
d- Steroid synthesis.

37. Favism is due to deficiency of:

a- Glucose -6- phosphatase.
b- Pyruvate kinase.
c- G-6-P-dehydrogenase.
d- Aldolase B.

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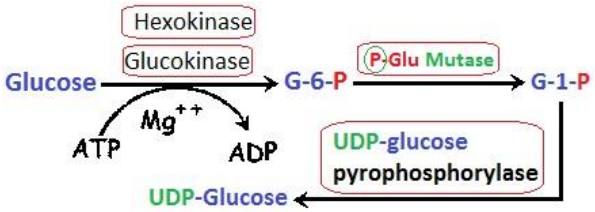
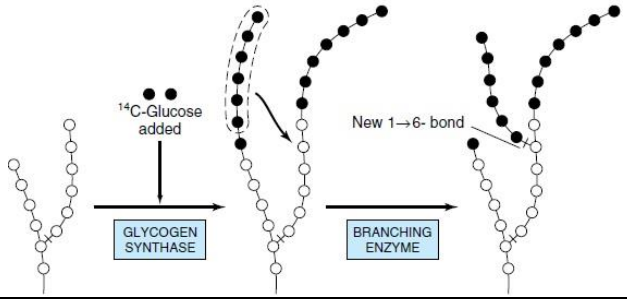
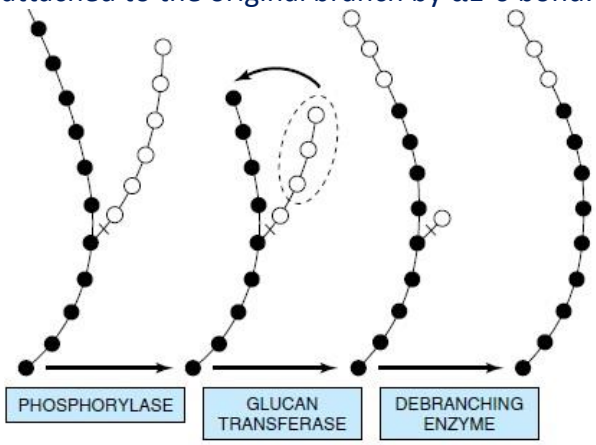
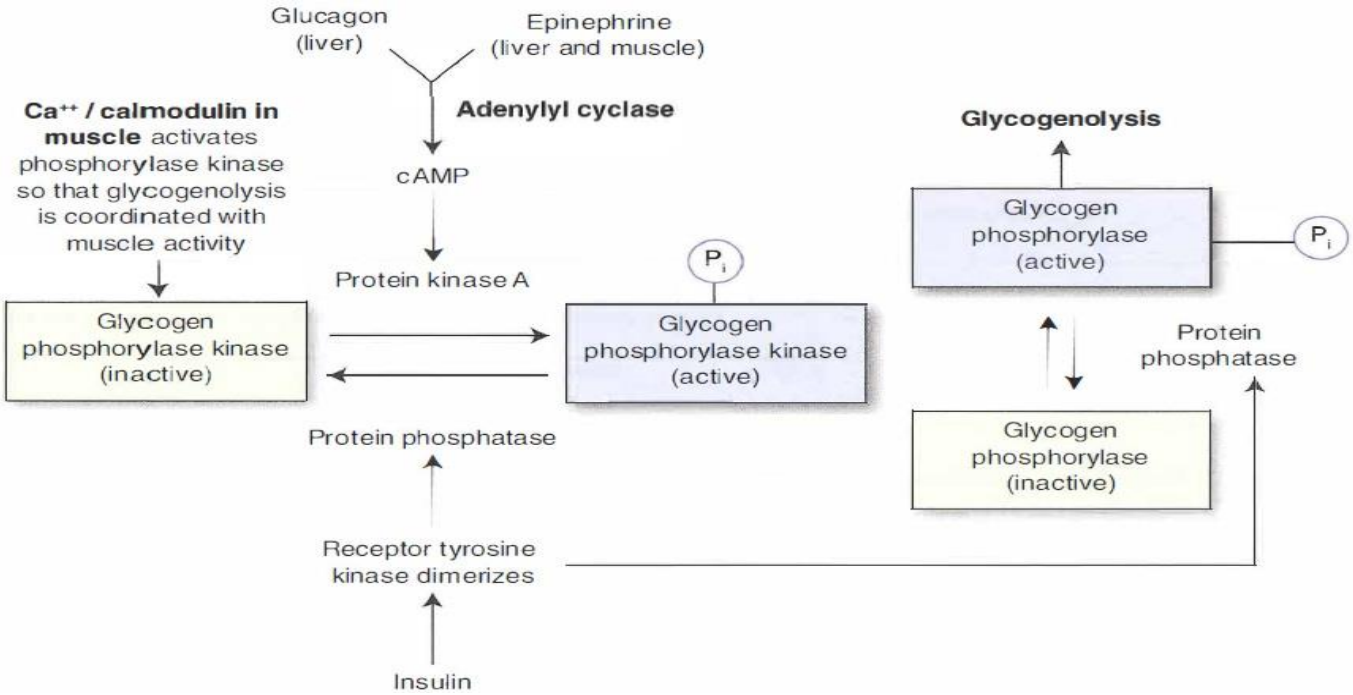
Glycogen Metabolism

	GLYCOGENESIS	GLYCOGENOLYSIS
Def	Formation of glycogen in liver and muscle.	Breakdown of glycogen into glucose (in liver) and lactate (in muscles)
Site	Cytoplasm in liver and muscle	Cytoplasm in liver and muscle
Steps	**1. Activation of Glucose to (UDP-Glucose):**  **2. Formation of glycogen primer which:** - Few molecules of glucose react with OH of tyrosine of a protein called glycogenin. **3. Glycogen synthase "Key enz."** - UDP-G molecules are added to glycogen primer causing elongation of the α1-4 branches up to 12-14 glucose units. **4. Branching enzyme:** -Transfers parts of the elongated chains (5-8 glucose residues) to the next chain forming a new α1-6 glycosidic bond.  	**1. Phosphorylase "Key enz.".** - Acts on α1-4 bonds, breaking it down by phosphorolysis. - It removes glucose units in the form of glucose-1-phosphate. - It acts on the branches containing more than 4 glucosyl units. **2. Transferase:** - When the branch contains 4 glucose units, **3** of them are transferred to a next branch by transferase enzyme leaving the last one. **3.Debranching enzyme:** Removes the last glucose unit that is attached to the original branch by α1-6 bond. 

Liver Glycogen	Muscle Glycogen
From bl. glucose, other Hexose & lactate	From blood only
120 gm. = 6%	350gm. = 1%
Correct blood glucose	ATP for muscle only
Contain G-6-phosphatase	NO G-6-phosphatase
Stimulated by Glucagon	NO effect

REGULATION OF GLYCOGENESIS AND GLYCOGENOLYSIS

There is a **coordinated** regulation of glycogenesis and glycogenolysis **i.e.** conditions **stimulate** glycogenolysis, **inhibit** glycogenesis at the same time and vise versa.



GLYCOGEN STORAGE DISEASES

Glycogen storage diseases	12 types, all resulting in abnormal glycogen metabolism and an accumulation of glycogen within cells.		**V**ery **P**oor **C**arbohydrate **M**etabolism.
Disease	**Findings**	**Deficient enzyme**	**Comments**
Von Gierke's disease (type I)	Severe fasting hypoglycemia, ↑↑ glycogen in liver, ↑ blood lactate, hepatomegaly, **Gout**	Glucose-6-phosphatase	
Pompe's disease (type II)	Cardiomegaly and systemic findings leading to early death	Lysosomal α-1,4-glucosidase (acid maltase)	**P**ompe's trashes the **P**ump (heart, liver, and muscle).
Cori's disease (type III)	Milder form of type I with normal blood lactate levels	Debranching enzyme (α-1,6-glucosidase)	Gluconeogenesis is intact.
McArdle's disease (type V)	↑ glycogen in muscle, but cannot break it down, leading to painful muscle cramps, myoglobinuria with strenuous exercise	Skeletal muscle glycogen phosphorylase	**M**cArdle's = **M**uscle.

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GLUCONEOGENESIS

DEFINITION

Gluconeogenesis is the formation of **glucose** from **non-carbohydrate** sources.

These sources include:

- Lactate.
- Pyruvate.
- Glycerol.
- Some amino acids.
- Propionate (in ruminants only).

SITE

A. Intracellular location: Cytosol & mitochondria.

B. Organ location: 1. Liver (90%).
2. Kidney (10%).

STEPS

The steps of gluconeogenesis are mainly the reversal of glycolysis, except for the three irreversible kinases which are replaced by the following enzymes:

Glycolysis	Gluconeogenesis
Glucokinase.	Glucose-6-phosphatase.
Phosphofructokinase -1.	Fructose 1, 6 bisphosphatase.
Pyruvate kinase.	Pyruvate carboxylase.
	Phosphoenol pyruvate carboxykinase.

1. Pyruvate to phosphoenol pyruvate:

- This conversion is done by dicarboxylic acid shuttle and needs 2 enzymes:
  a) Pyruvate carboxylase: present in mitochondria.
  b) Phosphoenol pyruvate carboxykinase: present in Cytosol.
- Pyruvate should pass first **from** Cytosol **to** mitochondria by special transporter.
- Pyruvate is then converted into oxaloacetate by pyruvate carboxylase (in the presence of biotin, CO_2 and ATP).
- The mitochondrial membrane is **im**permeable to oxaloacetate. So, oxaloacetate is converted to Malate by **(Malate dehydrogenase)**.
- Malate is transported to Cytosol, where it is converted again into oxaloacetate **(by Cytosolic Malate dehydrogenase)**.
- Oxaloacetate is converted into phosphoenol pyruvate by **(phosphoenol pyruvate carboxykinase)**.

N.B. : Pyruvate **never goes** in the course of citric acid pathway to reach Malate,
Because this pathway needs **insulin** and **other factors**.

2. Fructose 1,6 bisphosphate to fructose-6-phosphate:

This reaction is catalyzed by the enzyme **(fructose 1, 6 bisphosphatase)**.

3. Glucose-6-phosphate to glucose:

This reaction is catalyzed by the enzyme **(glucose-6-phosphatase).**

PATHWAYS FOR DIFFERENT SOURCES OF GLUCONEOGENESIS

A. gluconeogenesis from lactate:

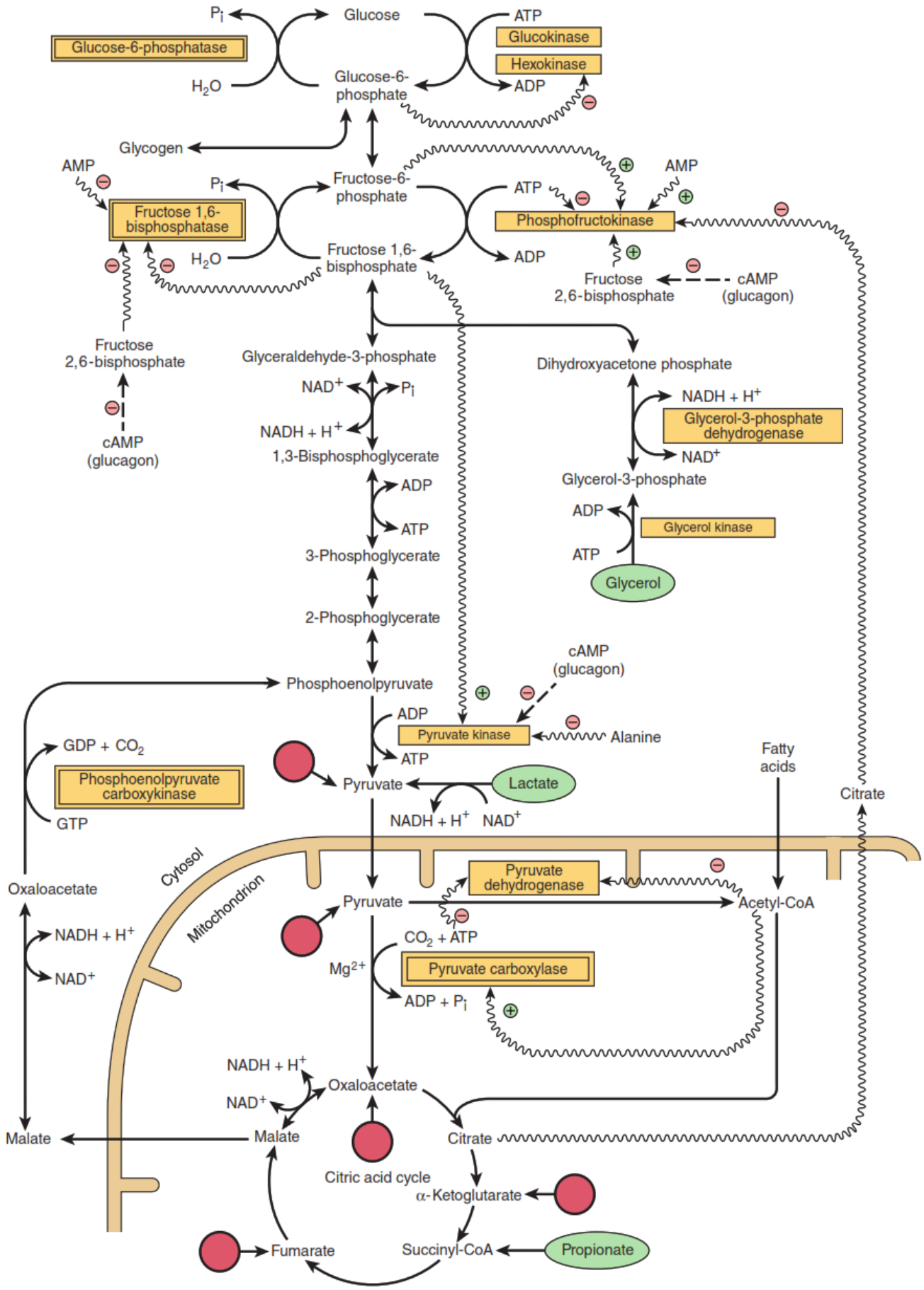
B. Gluconeogenesis from glutamate:

Glutamate is converted into **α-Ketoglutarate** by **transamination** reaction → **krebs**

D. Gluconeogenesis from Glycerol:

C. Gluconeogenesis from Propionic acid:

- This occurs only in **ruminants** and not in human.
- Propionic acid is converted into **Succinyl CoA** → **Malate** → common pathway.



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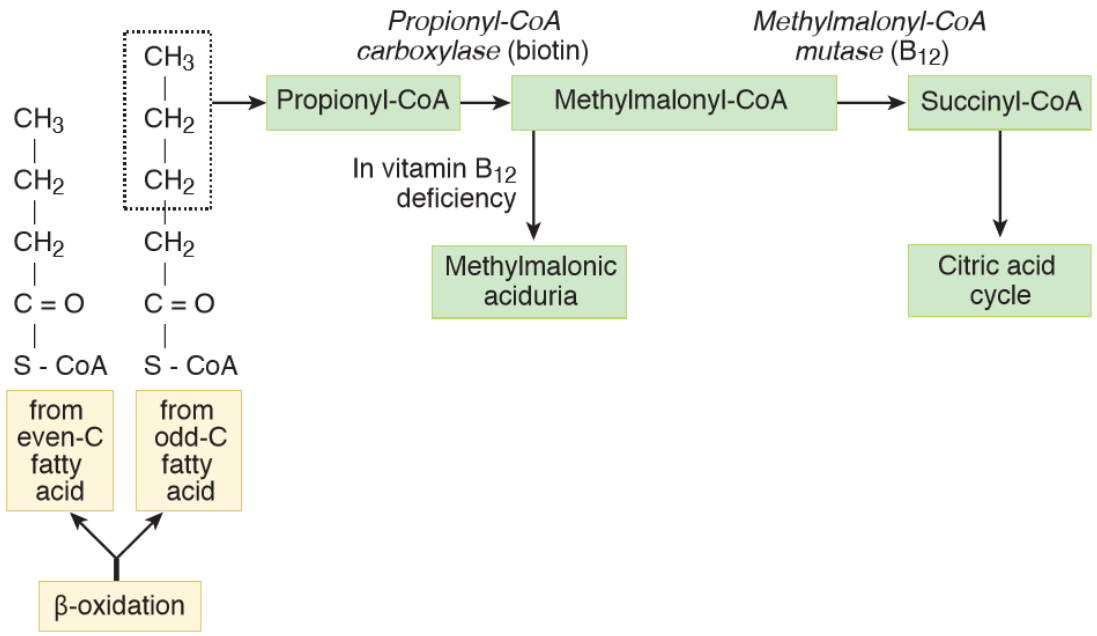

REGULATION OF GLUCONEOGENESIS

gluconeogenesis& glycolysis are reciprocally regulated

A. Hormonal regulation:

Glucagon (+)

- Secreted in response to hypoglycemia
- ↑ synthesis of gluconeogenesis enz.
- inhibit glycolysis.
- stimulate insulin secretion.

Cortisol (+)

- ↑ synthesis of gluconeogenesis enz.
- ↑ protein catabolism
- ↑glycogenic amino acids
- inhibit glycolysis.

Insulin (-)

- Secreted in response to hyperglycemia.
- inhibit of gluconeogenesis enzymes
- stimulate glycolysis.

B. Substrate regulation: Acetyl CoA and ATP

1. **Stimulate gluconeogenesis** by **inhibiting glycolysis** (through inhibiting **PFK-1**) and stimulate gluconeogenesis (by stimulating **fructose1, 6 bisphosphatase**).
2. Acetyl CoA also stimulates **pyruvate carboxylase** (gluconeogenesis)
   And inhibit **pyruvate dehydrogenase** (oxidation).

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MCQ

38. Gluconeogenesis is inhibited by:

a- Glucagon b- Growth hormone c- Insulin d- Glucocorticoids

39. All the following are key gluconeogenic enzymes EXCEPT:

a- Pyruvate carboxylase b- Phosphoenol pyruvate carboxykinase
c- Phosphofructokinase d- Glucose-6-phosphatase

40. How many ATP molecules are required to convert 2 molecules of pyruvate into glucose?

a- Two b- three c- Six d- Eight

41. All the following are substrates for gluconeogenesis Except

a- palmitic acid b- Lactic acid c- Alanine d- Glycerol

42. The hormone activating the enzyme glycogen phosphorylase is:

a- Epinephrine b- Insulin c- Growth hormone d- Glucocorticoids

43. Von Gierk's disease is characterized by the deficiency Of:

a- Glucose-6-phosphatase b- Glyceraldehyde-3-phosphate dehydrogenase
c- Phosphofructokinase d- Phosphorylase

44. As regards glycogen:

a- It is a highly branched polymer of aD glucose.
b. The glucose residues are united by a, and a, glucosidic bonds.
c- Glycogen stores in muscles are more than that of liver.
d- All of the above.

45. Glycogen phosphorylase is:

a- The key enzyme of glycogenesis. b- Activated by lcAMP.
c- Allosterically inhibited by ATP. d- Activated by insulin.

46. As regards Von Gierk's disease, all are correct, EXCEPT:

a- It is due to deficiency of G-6-phosohatase in the liver and kidneys.
b-There is fasting hypoglycemia.
c- There is hyperlipidemia and ketosis.
d- There is hypouricemia.

47. All gluconeogenic enzymes are present in cytosol, EXCEPT:

a- G-6-phosphatase.
b-Pyruvate carboxylase.
c- PEP carboxykinase.
d- Aldolase A.

48. One of the following cannot act as a precursor for gluconeogenesis

a- Lactate. b- Glycerol c- Alanine. d. Acetyl COA.

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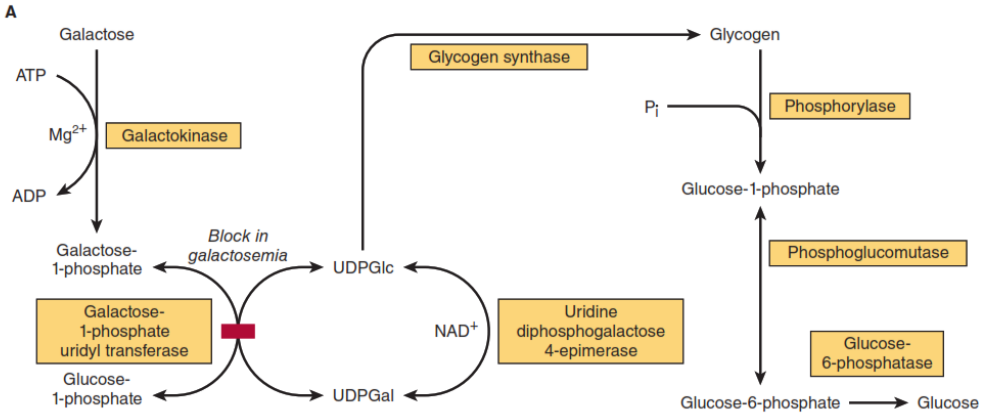
GALACTOSE METABOLISM

IMPORTANCE OF GALACTOSE: IN THE FORM OF UDP-GALACTOSE

A. Synthesis of lactose (= Milk sugar).
B. Synthesis of glycolipids (cerebrosides).
C. Synthesis of glycoproteins and proteoglycans.
D. Synthesis of glycosaminoglycans.

CONVERSION OF GALACTOSE INTO GLUCOSE

A. Site: Liver.
B. Steps:



GALACTOSEMIA

Definition: It is increase blood galactose concentration due to inability to metabolize galactose.
Causes: Inherited enzyme deficiency of:

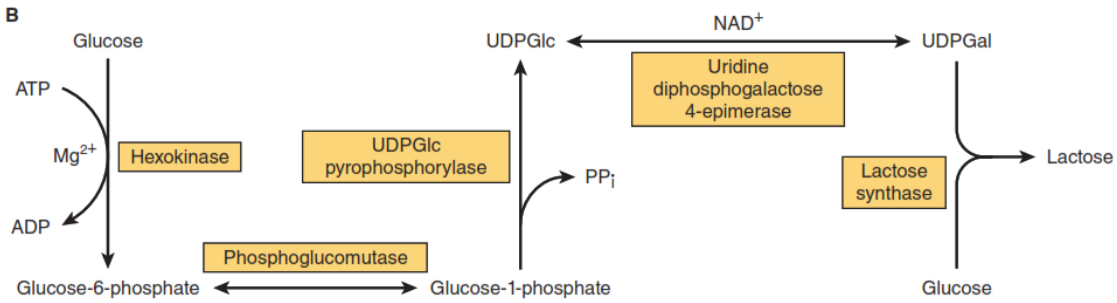
1. Galactokinase.
2. Galactose-1-P uridyl transferase:
3. Epimerase.

Effect: **a) Infantile Cataract** = opacity of eye lens:
Galactose in the eye is reduced by an enzyme called **Aldose reductase** into galacticol, which accumulates causing cataract.
b) Liver failure.
c) Mental retardation.
d) Galactosuria: excretion of galactose in urine.

CONVERSION OF GLUCOSE INTO GALACTOSE IN MAMMARY GLAND AND LACTOSE SYNTHESIS

Lactose is a disaccharide formed of **β -galactose** attached to **α-glucose** by **β1-4 bonds**. It is called **milk sugar**

Steps: **1.** Glucose is first converted into UDP-galactose.
2. UPD-Galactose reacts with a molecule of glucose in the presence of enzyme to form lactose.



FRUCTOSE METABOLISM

DIETARY SOURCES OF FRUCTOSE

- **Sucrose:** (table sugar): Hydrolysis of sucrose → glucose and Fructose
- **In honey and in many fruits and vegetables** as a monosaccharide.

IMPORTANCE OF FRUCTOSE

A. Energy production: 15% of daily energy is derived from fructose.

B. Fructose is the major energy source for **spermatozoa** in the **seminal vesicle**.

METABOLISM OF FRUCTOSE

A. In the liver:

1. Liver contains **fructokinase** enzyme, which phosphorylates fructose into fructose-1-phosphate.
2. Fructose-1-phosphate by **aldoase B** enzyme → Dihydroxyacetone phosphate + glyceraldehyde.
3. Glyceraldehyde → glyceraldehydes-3-phosphate.
4. Glyceraldehyde-3-p + Dihydroxyacetone may undergo:
   a) **Glucose formation** (gluconeogenesis) main pathway.
   b) **Oxidation to pyruvate** (glycolysis).

B. In extra-hepatic tissues:

1. Because fructokinase is not available in muscles and adipose tissue, fructose is metabolized by Hexokinase and other enzymes into pyruvate → oxidation

C. In the testis (seminal vesicle, lens, peripheral nerves and renal glomeruli:

1. Glucose is converted into fructose through sorbitol formation:
2. Fructose is the main nutrient for sperms.
3. Deficiency of fructose in semen correlates with male infertility.

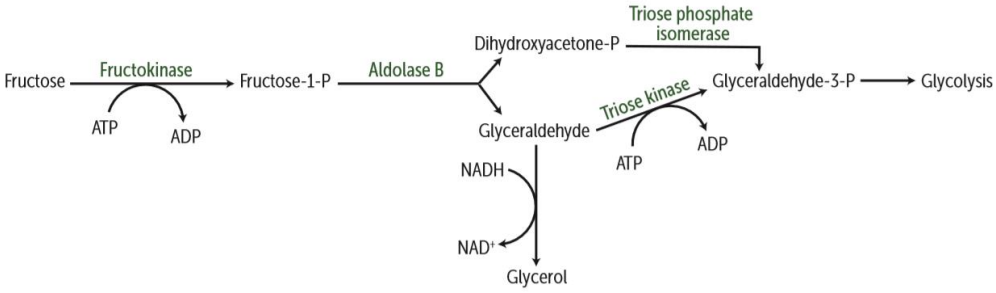
GENETIC DISORDERS OF FRUCTOSE METABOLISM

1- Essential fructosuria:

1. **Cause:** Due to deficiency of **Fructokinase** enzyme.
2. **Effect:** Not serious condition. The excess accumulated fructose is lost in urine.

2- Hereditary fructose intolerance.

1. **Cause:** Due to deficiency of **Aldolase-B enzyme**. This leads to accumulation of Fructose-1-phosphate.
2. **Effect:** the accumulation of Fructose-1-phosphate leads to:
   a) Damage of liver and kidney tissues → Liver and kidney failure.
   b) Inhibition of Phosphorylase enzyme. This leads to inhibition of glycogenolysis and fasting hypoglycemia.



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MCQ

49. All are true as regards fructose intolerance

a- Defective enzyme is aldolase-B
b- Fructose-I-phosphate accumulates
c- Glycogen phosphorylase is inhibited
d- Urine is free from fructose

50. Features of galactosemia include the following

a- Cataract
b- Hepatosplenomegaly
c- Mental retardation
d- Hemolytic anemia

51. The commonest deficient enzyme in Galactosemia is:

a- Galactokinase
b- Galactose -1- P uridyl transferase
c- UDP transferase
d- Galactose -l phosphatase.

52. Hereditary fructose intolerance is a condition caused by a deficiency of:

a- Phosphofructokinase.
b- Fructokinase.
c- Aldolase B.
d- Fructose 6-phosphatase.

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BLOOD GLUCOSE

PLASMA GLUCOSE LEVELS

A. Fasting level = 65-110 mg/dl (3.6-6.1 mmol/L)
B. One hour after carbohydrate meal = 120-150 mg/dl (6.7-8.3 mmol/L).
C. Two hours after carbohydrate meal (PP) = 65-140 mg/dl (3.6-7.8 mmol/L).

REGULATION OF BLOOD GLUCOSE LEVEL

Hormonal regulation	Organ regulation
Insulin **the only hormone which** reduces blood glucose level through: Stimulation of: - **Glucose uptake by cell.** - **Glucose oxidation.** - **Glycogenesis.** - **Lipogenesis.** Inhibition of: - **Glycogenolysis.** - **Gluconeogenesis.**	**Liver** **During fasting:** - Glycogenolysis. - Gluconeogenesis. - Ketogenesis. **After carbohydrate meal:** **60%** of glucose is taken up by liver, and converted into glucose-6-phosphate, by Glucokinase enzyme: - **Glucose-6-phosphate will undergo one of the following fate in the liver:** - (Glycogenesis) - (lipogenesis).
Glucagon Stimulation of: - **Glycogenolysis** - **Gluconeogenesis.**	**Kidney** - Glucose is completely reabsorbed by kidney until reaching renal threshold (Average 180 mg/dl). - Then appears in urine (glycosuria). **Low renal threshold:** - Normally in some persons due to defective tubular enzymes for Glucose reabsorption (diabetes innocence). - In **20%** of pregnant females. **High renal Threshold:** - In Elderly people due to reduced glomerular filtration rate. - In cases of diabetes with renal damage.
Catecholamines Stimulation of: - **Glycogenolysis**	
Glucocorticoids Stimulation of: - **Gluconeogenesis.** - **↑ Ptn catabolism→↑a.a.**	
Growth hormone Inhibition of: **glucose uptake by cells.** Blocks: **insulin action at cell membranes.**	

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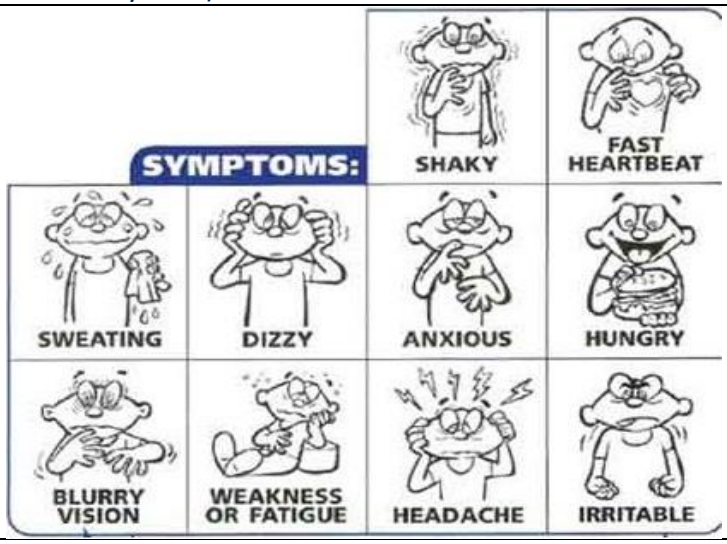
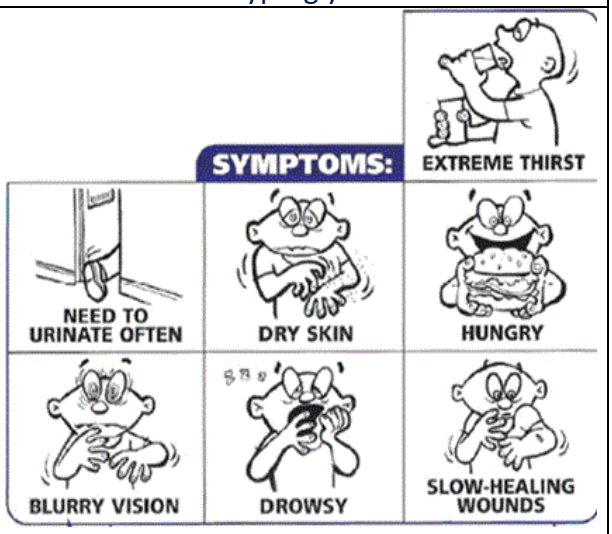
VARIATIONS IN BLOOD GLUCOSE

Hypoglycemia	Hyperglycemia
Definition: **Decrease of blood glucose concentration below normal fasting average concentration: less than 65 mg/dl.**	Definition: It is the rise of blood glucose above normal average level.
Mechanism: Hypoglycemia activates: 1- α- Cells of islets of Langerhans → ↑Glucagon + ↑Glycogenolysis →↑Blood glucose. 2- Receptors in hypothalamus: This stimulates Secretion of epinephrine (mediated by autonomic nervous system).	Causes: **1.** Diabetes mellitus: CC **2.** In patients receiving intravenous fluid containing glucose. **3.** Temporarily in severe stress. **4.** After cerebro-vascular accidents. **5.** Disturbance in hyperglycemic hormones.
	

Types and causes of hypoglycemia:

Types	Organ or cause	Examples
Fasting	**- Pancreas**	**Insulinoma.**
	- Other endocrine gland	**Adrenocortical hypofunction.**
	Liver	**Prolonged starvation.**
Stimulative	**-Drugs and Poisons**	**↑insulin or ↑sulphonylurea.** **- Liver poisons**
	-Postgastrectomy **- Leucine** **- hypersensitivity**	
	- Inborn errors of metabolism	**- Galactosemia** **- fructosemia** **- Von Gerkie's D**

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CHO DISEASE

	DISEASE	DEFICIENCY OF	EFFECT
LACTOSE	**1. Lactose intolerance** Maybe: 1- congenital (Rare) 2- Acquired (Common	**Lactase enzyme**	**1-** Osmotic pressure → Dehydration & causing diarrhea. **2-** ↑ fermentation of lactose by bacteria → Abdominal cramps.
GLYCOLYSIS	**1- Hemolytic anemia**	Pyruvate kinase Hexokinase	↓rate of Glycolysis → ↓production of ATP
	2-Lactic acidosis	**Causes** of lactic acidosis: **a-** Increase formation of lactate **b-** Decrease utilization of lactate.	
HEXOSE PHOSPHATE PATHWAY OR (PPP)	**1- Favism:** (Hemolytic anemia) In the form of severe jaundice & ↓HB conc. **Precipitating factors:** **a-** Oxidant drugs e.g. sulpha & Primaquine Anti-malarial, **b-** Fava beans.	Glucose -6-phosphate dehydrogenase	**a-** ↓NADPH+H→↓ reduced glutathone→ accumulation of H_2O_2 →Hemolysis of RBCs. **b-** H_2O_2 conversion HB into Met-hemoglobin → the RBC membrane fragility.
	2- Chronic bacterial infection	NADPH+H^+ oxidase	
URONIC ACID PATHWAY	**Essential pentosuria**	L- xylulose reductase	pentosuria
GLYCOGEN STORAGE DISEASES	**Von Gerkie's disease (type I)**	Glucose-6-phosphatase (# gluconeogenesis)	Severe fasting hypoglycemia, ↑ glycogen in liver, ↑ blood lactate, hepatomegally, Guat
	Pompe's disease (type II)	Lysosomal α-1,4-glucosidase (acid maltase)	Cardiomegaly and systemic findings leading to early death
	Cori's disease (type III)	Debranching enzyme (α-1,6-glucosidase)	Milder form of type I with normal blood lactate levels **Gluconeogenesis is intact**.
	McArdle's disease (type V) muscle	Skeletal muscle glycogen Phosphorylase	↑ glycogen in muscle, but cannot break it down, leading to painful muscle cramps, myoglobinuria with strenuous exercise
FRUCTOSE	**Essential**	Fruktokinase	fructosuria
	Fructose intolerance	Aldolase-B	- Liver and kidney failure - fasting hypoglycemia

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CHAPTER 6

Lipid Metabolism

CHAPTER MAP

Lipids Metabolism

Feeding state واحنا واكلين هيكون في انسولين	Fasting state واحنا صايمين
1- Fatty acid synthesis 2- Lipogenesis 3- Cholesterol synthesis 4- Conjugated lipid synthesis	1- Lipolysis 2- Fatty acid oxidation 3- Ketogenesis 4- Ketolysis

FATE OF ABSORBED LIPIDS

A. After fatty meal plasma shows a **milky appearance**. This due to venous blood contains excess **chylomicrons** after absorption.

- Excess chylomicrons stimulate **mast cells** to produce **heparin**. Heparin then stimulates the lining epithelium of blood vessels of **heart**, **lungs**, **spleen** and **adipose tissue** to produce an enzyme called: **lipoprotein lipase** (plasma clearing factor).
- Lipoprotein lipase enzyme will act on **triacylglycerols** of chylomicrons, converting them into glycerol and free fatty acids.

B. Glycerol and **fatty acids** are taken up by different tissues for the following fate:

1. **Formation of depot fat (adipose tissue).**
   a) It is formed mainly of Triacylglycerols **b)** It is present in fat cells of adipose tissue.
2. **Oxidation for production of energy:**
   a) Fatty acids: Converted into **acetyl CoA** that is oxidized in **citric acid cycle**.
   b) Glycerol: Converted into **glycerol-3-phosphate** (by glycerol kinase). This is then converted into **DHAP**. The later will undergo oxidation in **glycolysis.**
3. **Glucose formation by gluconeogenesis:**
   a) Glycerol → Glucose.
   b) Odd number fatty acids oxidation → Propionyl CoA → Glucose.
4. **Synthesis of biologically active compounds:** e.g. different **steroids** and **eicosanoids**
5. **Synthesis of tissue fats** (structural cellular fats).

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STORAGE AND MOBILIZATION

- Body lipids are of 4 types: tissue lipids, adipose tissue (depot fat), plasma lipoproteins and bone marrow lipids.

Tissue lipids	*Adipose tissue (depot fat)*	
	White adipose tissue	**Brown adipose tissue**
- These lipids enter in the structure of body cells as cell membrane and mitochondria. *- Tissue lipids never oxidized to give energy.*	**a) Composition:** **1) Triacyiglycerols:** main content that contain saturated and unsaturated fatty acids. This makes depot fat in a fluid state at body temperature. **2) Little phospholipids and cholesterol**. **b) Site:** **1)** Under skin and in the breast. **2)** Around important organs e.g. kidney. **3)** In the omentum and mosentry. **c) Sources:** **1)** Absorbed fat. **2)** Carbohydrate. **d) Functions:** depot fat is important for: **1) Energy production:** During fasting, the triacylglycerols stored in depot fat provide the body with free fatty acids that oxidize to give energy. **2) Fixation of some organs** e.g. kidney. Heat insulator around the body. **4) Production of vitamin D_3:** by exposure of skin to ultraviolet rays	**a)** Certain areas of adipose tissue appear **brown** as they contain high content of **mitochondria, cytochromes** and well developed **blood supply**. **b) Function:** Production of heat. They contain a protein called Thermogenin. This protein acts as **Uncoupler** of oxidative phosphorylation → ↓ATP production and ↑heat generation. **c) Site:** common in animals exposed to cold atmosphere for warmness: It is little in human, especially in obese persons.

LIPOLYSIS

DEFINITION hydrolysis of Triacylglycerols in adipose tissue into glycerol and fatty acids.

STEPS

Lipolysis is carried out by a number of lipase enzymes, which are present in adipose tissue. These are

1. Hormone sensitive triacylglycerol lipase.
2. Diacylglycerol lipase.
3. Monoacylglycerol lipase.

FATE OF PRODUCTS OF LIPOLYSIS

1. **Fate of fatty acids**
   - **a)** Oxidation by tissue to give energy.
   - **b)** Fatty acids may remain in adipose tissue to be re-esterified into TAG again.
2. **Fate of glycerol:** Glycerol may diffuse to blood and then taken up by the liver to give:
   1) Glucose by gluconeogenesis. 2) Pyruvate by glycolysis.
   3) Triacylglycerols by lipogenesis.

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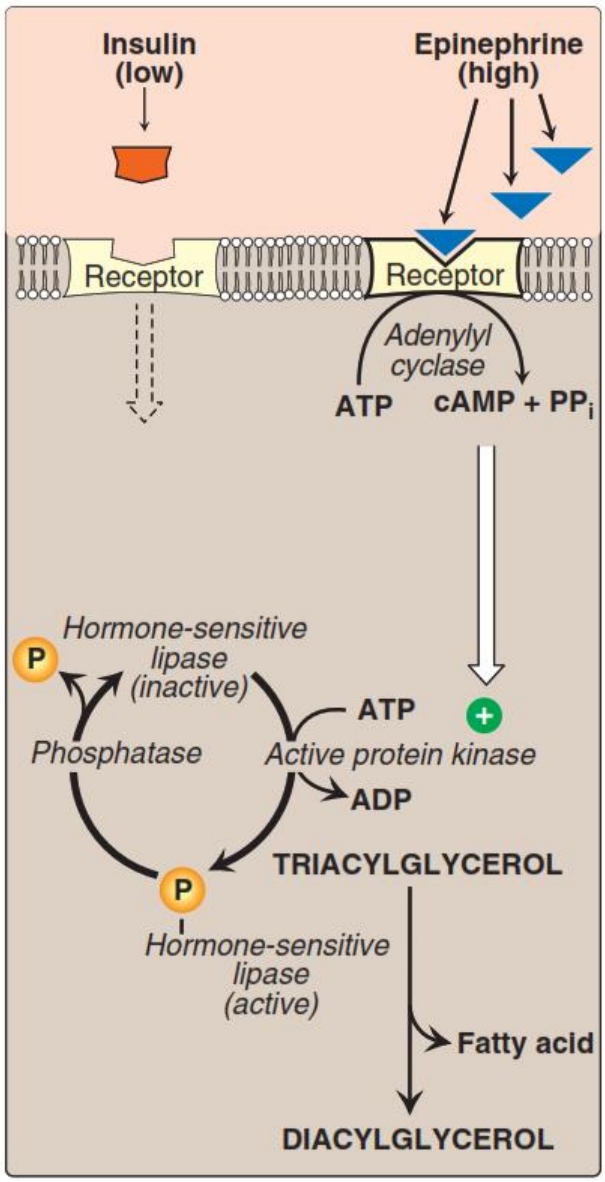
Regulation of Lipolysis

The key enzyme controlling Lipolysis is the Hormone sensitive triacylglycerol lipase. It exists in 2 forms: active (**Phosphorylated**) and inactive (**dephosphorylated**)

Causes of excessive Lipolysis: In conditions where the need for energy is increased (low insulin and high glucagon):

1. Starvation.
2. Diabetes mellitus.
3. Low carbohydrate diet.
4. In certain infectious diseases as in tuberculosis (due to high catabolic state)



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Fatty acids oxidation

- 3 Different pathways for fatty acid oxidation are present: α, β and ω

β-OXIDATION

Site

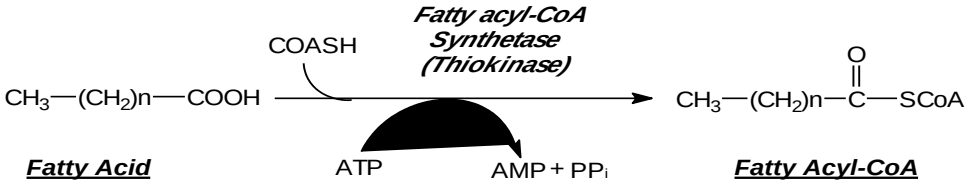
1. **Intracellular location:** Mitochondria
2. **Organ location:**

a) Liver, kidney, heart and skeletal muscles.

b) β-Oxidation **never occur** in **brain** (*can't pass BBB*) and **RBCs** (*no mitochondria*).

Mechanism

1- Activation of Fatty Acids.



Activation Of A Fatty Acid.

2- Transport of Acyl-CoA from Cytosol into Mitochondria by Carnitine Shuttle:

a) Structure of Carnitine:

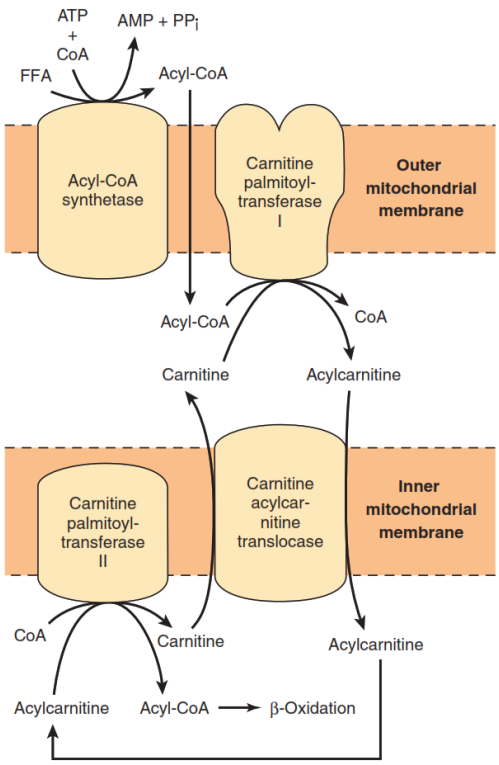
Carnitine is β-hydroxy-γ-trimethyl ammonium butyric acid. It is derived from lysine amino acid.

b) Function of Carnitine:

It transports long chain acyl CoA inside the mitochondrial matrix where enzymes for β-oxidation are present.

c) Steps of shuttle three enzymes are involved

1. **Carnitine acyl transferase I** (Carnitine palmitoyl transferase I)
   - It is present in the outer mitochondrial membrane.
   - It transfers the **acyl group** from acyl CoA to Carnitine to form **acyl Carnitine**.
2. **Carnitine acylcarnitine translocase:**
   - It is present in the inner mitochondrial membrane.
   - It transports acyl Carnitine across inner mitochondrial membrane (in exchange with Carnitine).
3. **Carnitine acylcarnitine transferase II** (Carnitine palmitoyl transferase II).
   - It is present in the inner mitochondrial membrane.
   - It transfers the acyl group from acyl Carnitine to form **acyl CoA** again.



3. Unsaturation of fatty acids: Catalyzed by fatty acyl CoA dehydrogenase enzyme.

4. Hydration: Catalyzed by enoyl CoA hydratase enzyme.

5. Oxidation: Catalyzed by β-hydroxy acyl CoA dehydrogenase enzyme.

6. Splitting (Cleavage) step: Catalyzed by Acyl CoA acyl transferase (thiolase) enzyme.

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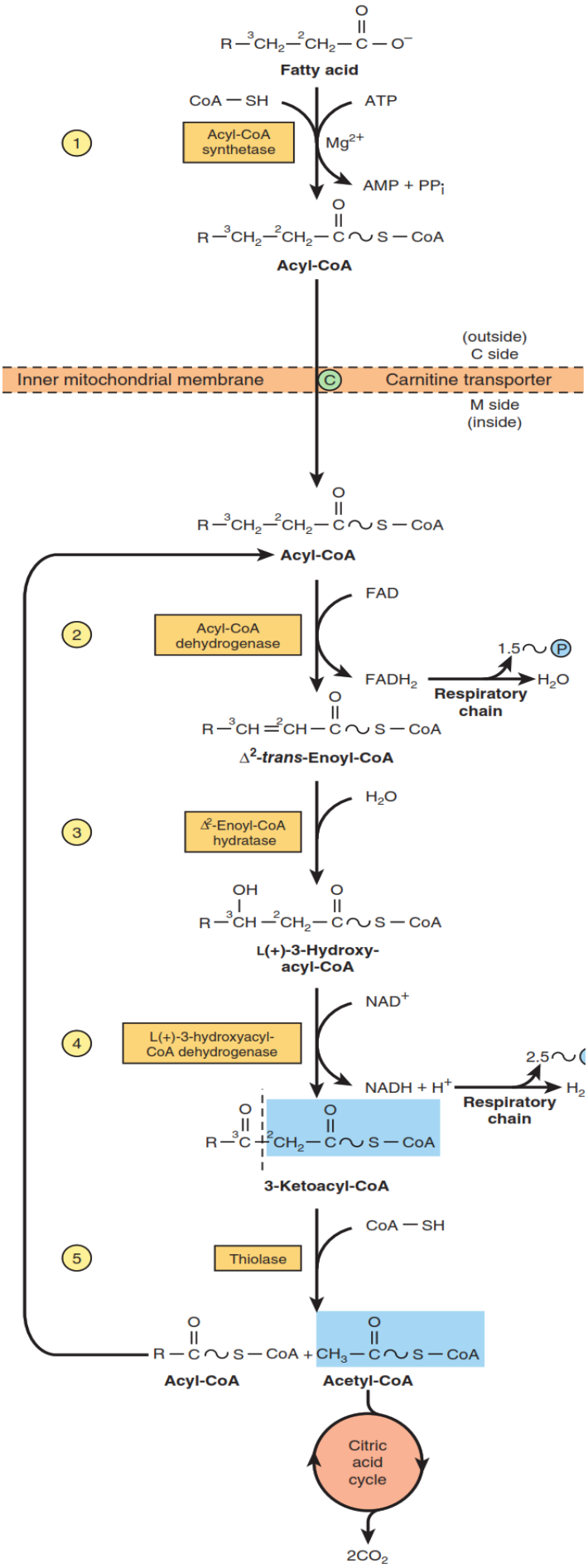

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ENERGY PRODUCTION OF β -OXIDATION

- Calculation formula of energy production of oxidation of any fatty acids:
- Oxidation of one molecule of acetyl CoA in citric acid cycle gives 12 ATP.
- In each turn: **1 $FADH_2$** → 2ATP **1 NADH+H** → 3 ATP = **5 ATP**

= **{(N/2 - 1) x 5 ATP} + {N/2 x 12 ATP} - 2 ATP**

-Two high energy phosphate bonds are utilized in the first reaction. Catalyzed by (acyl CoA synthetase) which occurs for one time only.

e.g. **palmitic acid** (16 carbons):

= **{(16/2 - 1) x 5 ATP} + {16/2 x 12 ATP} - 2 ATP**

= **{(35 ATP} + {96ATP} - 2 ATP =** 129 ATP

IMPORTANCE (FUNCTIONS) OF β -OXIDATION:

1. **Energy production** e.g. palmitic acid produces 129 ATP.
2. **Production of acetyl CoA:** which enter in many pathways.
3. **Ketone bodies formation:** Acetoacetyl CoA is the last 4 carbons product in the course of β-oxidation of even numbered fatty acids. It may be converted into acetoacetate; one of ketone bodies (see later).

OXIDATION OF ODD NUMBER FATTY ACIDS:

1. They are oxidized by **α-oxidation** till a **Propionyl CoA**, (3 carbons) is produced. Then Propionyl CoA is converted to **Succinyl CoA**

UNSATURATED FATTY ACIDS

- Their oxidation requires **new** enzymes in addition to the four enzymes.
- The pathways differ depending on the position in which the double bond is located.

a. **For fatty acids that contain a double bond at an odd carbon number** (e.g., between carbons 9 and 10), b-oxidation occurs until the double bond of the unsaturated fatty acid reaches position 3 of the acyl CoA. At this point, an isomerase will convert the cisD3 double bond to a transD2double bond. The normal steps of b-oxidation can then proceed.

b. **For fatty acids that contain a double bond at an even carbon position** (e.g., between carbons 12 and 13), b-oxidation occurs until the double bond of the unsaturated acid reaches position 4 of the acyl CoA.
After the acyl CoA dehydrogenase creates the trans double bond between carbons 2 and 3, the enzyme 2,4-dienoyl CoA reductase reduces the two double bonds into one, generating a trans D3 double bond. The trans D3 double bond is then isomerized to transD2,so that the normal steps of b-oxidation can then proceed.

α-OXIDATION

- This type of oxidation occurs in α- position and characterized by:
  1. It is a mechanism mainly for oxidation of branched chain fatty acid, which are methylated at β position.
  2. It is specific for oxidation of Phytanic acid (3, 7, 11, 15 tetramethyl palmitic acid), present in plant foodstuffs.
  3. It is minor pathway for fatty acid oxidation, occurs mainly in brain and nervous tissues.
- In α-oxidation, there is **one carbon** atom removed at a time from α position
- It does not **require CoASH** and does **not** generate high energy phosphate.

REFSUM'S DISEASE:

- **Def:** inherited deficiency of enzymes responsible for α-oxidation of Phytanic acid.
- **Manifestation:** accumulation of Phytanic acid in nervous tissue and produce nervous damage e.g. **deafness** and **blindness**.

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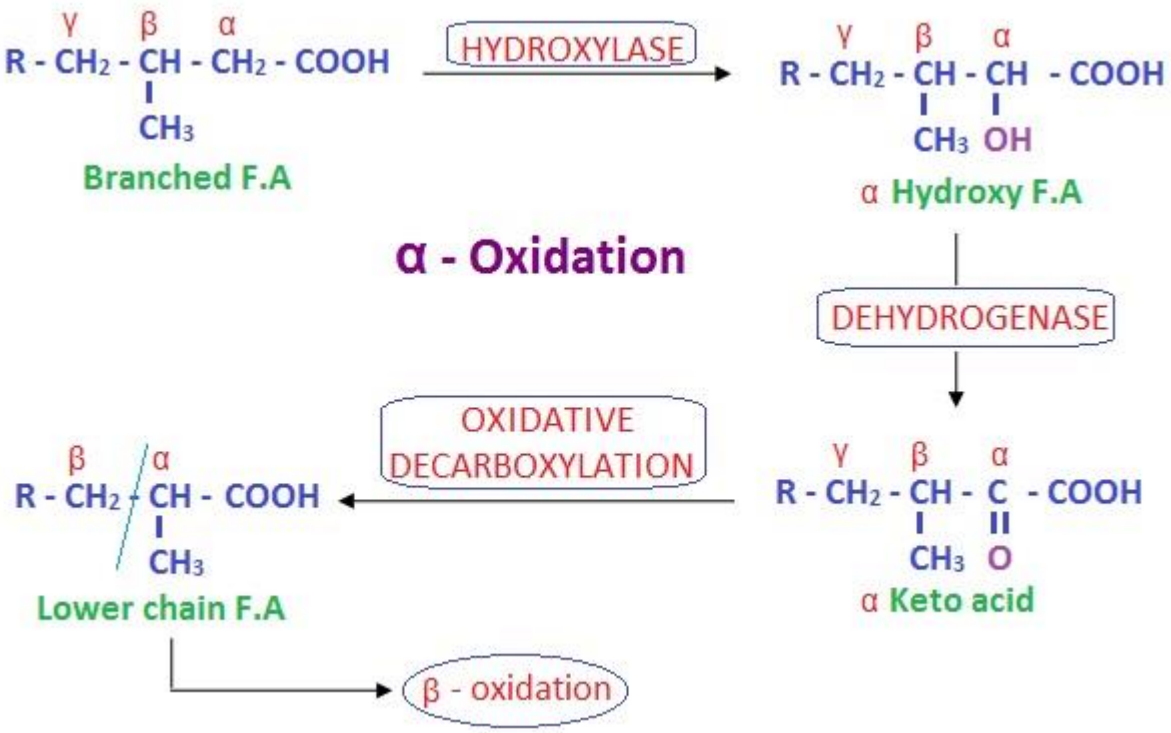
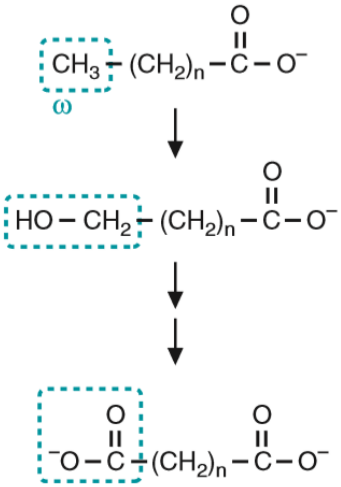


ω-OXIDATION

- It is oxidation of terminal **CH_3** group (ω carbon) of fatty acid.
- This produces **dicarboxylic fatty** acids. By **β**-oxidation they are converted to adipic acid (6 carbons) and suberic acid (8 carbons).
- ω-Oxidation is a minor pathway for fatty acid oxidation and catalyzed by hydroxylase enzymes of **cytochrome P_{450}**



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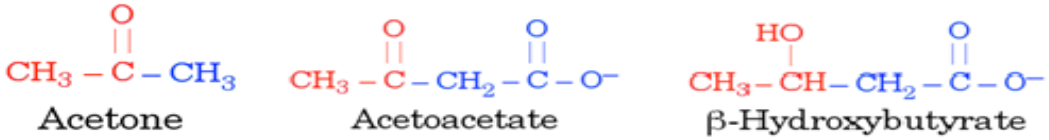
KETONE BODIES

Definition

these are 3 compounds formed by the liver and include:



FUNCTIONS OF KETONE BODIES

- **Source of energy:** They are converted into acetyl-CoA which is oxidized in tricarboxylic acid (TCA) cycle.
- Skeletal muscles, cardiac muscles, kidneys and most of tissues can use ketone bodies as a source of energy in **prolonged fasting** and **starvation**.
- **Brain tissue** can also oxidize ketone bodies within 5 to 6 days of starvation.
  Note: brain never oxidizes fatty acids.
- **Liver** does not contain enzymes for ketone bodies oxidation (**ketolysis**). Thus liver cannot oxidize them.

	Ketogenesis	Ketolysis
location	Organ: Liver (partial oxidation)	Extra-hepatic tissues
	Intracellular	Mitochondria
Precursor	Acetyl CoA from: (F.A oxidation & Ketogenic a.a)	
Steps	**1.** Formation of **acetoacetyl CoA**: **a)** From condensation of 2 acetyl CoA. **b)** Acetoacetyl CoA may also be derived from β-oxidation of F.A **2.** Formation of **HMG-CoA** By condensation of third molecule of **acetyl CoA** in the presence of HMG CoA synthase **3.** Formation of **acetoacetate** by HMG CoA lyase. **4.** Acetoacetate is either: a) Spontaneously decarboxylated into **acetone** b) Reduced by hydroxybutyrate dehydrogenase into **β-hydroxybutyrate.**	- **Acetone** is volatile and removed in the expired air. - **β-Hydroxybutyrate** is converted into acetoacetate by hydroxybutyrate dehydrogenase - **Acetoacetate** is then activated into Acetoacetyl CoA by: a) **Thiophorase** in the presence of Succinyl CoA. **b) Acetoacetate synthetase** in the presence of ATP. - **Acetoacetyl CoA** is split into two molecules of **acetyl CoA** which are oxidized in TCA
Regulation	**1. After meal:** insulin is secreted, and this inhibits Lipolysis and in turn inhibit Ketogenesis. **2. During fasting:** glucagon. This stimulates Lipolysis and in turn Ketogenesis.	

Conditions that increase Ketogenesis:

1. Fasting and starvation. 2. Carbohydrate poor diet. 3. High fat diet. 4. Diabetes mellitus
5. ↑ muscular exercise. 6. pregnancy

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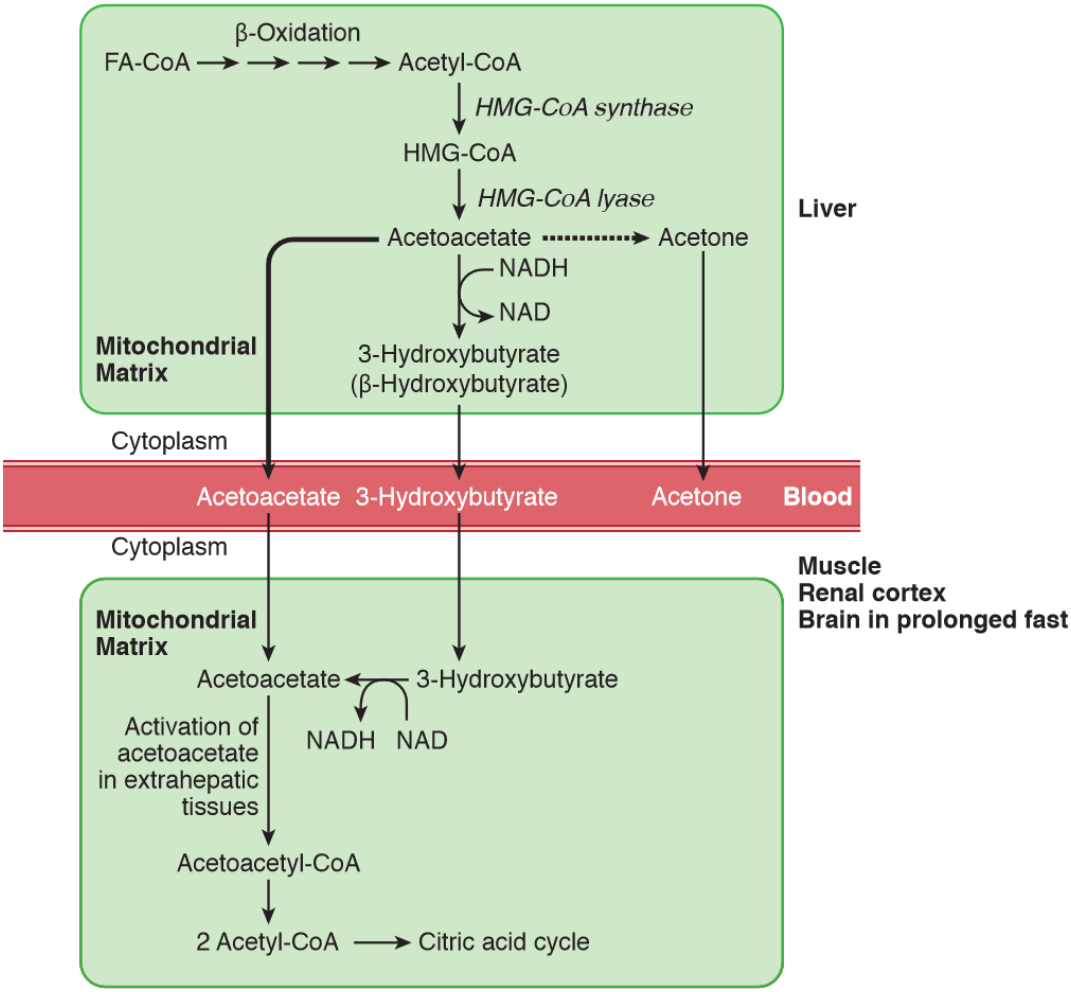

BLOOD KETONE BODIES AND KETOSIS

- **Blood ketone bodies** concentration is less than **3** mg/dl.
- **Ketonemia:** is the increase of blood ketone bodies above normal concentration.

1. It occurs when the rate of **Ketogenesis** is greater than the rate of **ketolysis**.

- **Urine ketone bodies:** is less than **40** mg/day.
- **Ketonuria:** is the increase of urine ketone bodies above normal concentration.

1. It usually occurs with Ketonemia. 2. Concentration may reach 5000 mg/day.

CAUSES OF KETONEMIA AND KETONURIA

1. Starvation. **2.** Severe diabetes mellitus. **3.** Hypercatabolic states e.g. diarrhea

KETOSIS = (KETOACIDOSIS)

- **Definition:** It is a condition of metabolic acidosis results from Ketonemia.
- **Mechanism: a)** An increase of ketone bodies in the blood is neutralized by blood buffers mainly bicarbonate (HCO3).
  b) Bicarbonate will be depleted and this leads to decreased blood pH (acidosis).
- **Effects of acidosis:**

a) Acidosis causes dizziness, loss of concentration...etc.

b) Acidosis causes transfer of **potassium** (K^+) ions from intracellular fluid to blood leading to (↑ K^+) hyperkalemia.

- **Ketotic coma:** In severe cases of ketosis as in uncontrolled diabetes mellitus, coma may be developed and the condition may be fatal.

Lipogenesis

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FATTY ACID SYNTHESIS

- There are 2 mechanisms for fatty acids synthesis: cytoplasmic and microsomal.

❖ CYTOPLASMIC SYSTEM (extra-mitochondrial) or (de novo)

- The main product of this pathway is **palmitate** (16_C).

SITE

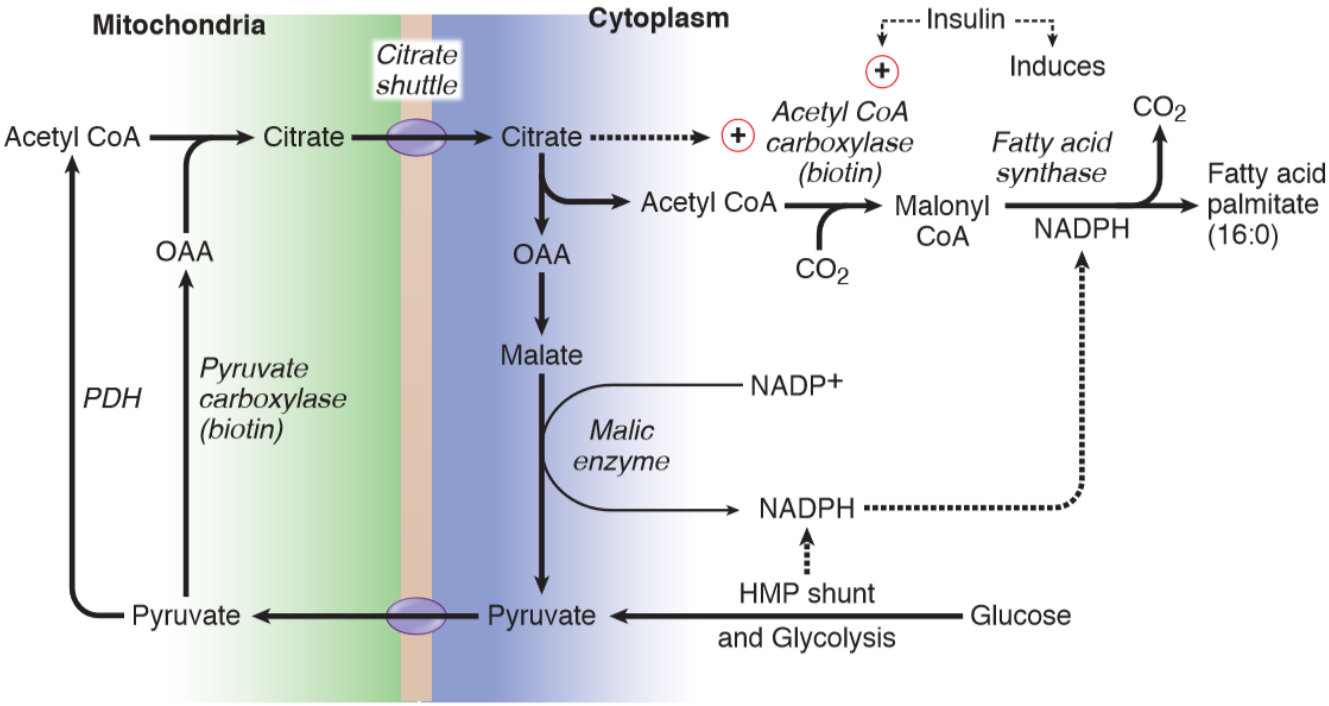
1. **Intracellular location:** Cytosol.
2. **Organ location:** Many tissues including liver, adipose tissue, lung and kidney.

REQUIREMENTS

❖ This pathway needs the following substrates: **acetyl CoA**, **NADPH+H** and group of enzymes called **fatty acid synthase complex**.

1. Acetyl CoA:

- It is provided mainly by glucose through pyruvate (glycolysis).
- Acetyl CoA is formed in mitochondria and fatty acid synthesis occurs in cytosol.
- The acetyl CoA cannot diffuse to cytosol because mitochondrial membrane is impermeable to it.



2. NADPH+H: It is provided by 3 sources:

a) Pentose phosphate pathway.

b) Action of cytoplasmic (Isocitrate dehydrogenase) on Isocitrate. It is similar to mitochondrial one but it uses $NADP^+$ as hydrogen carrier.

c) Action of malic enzyme on malate to produce pyruvate.

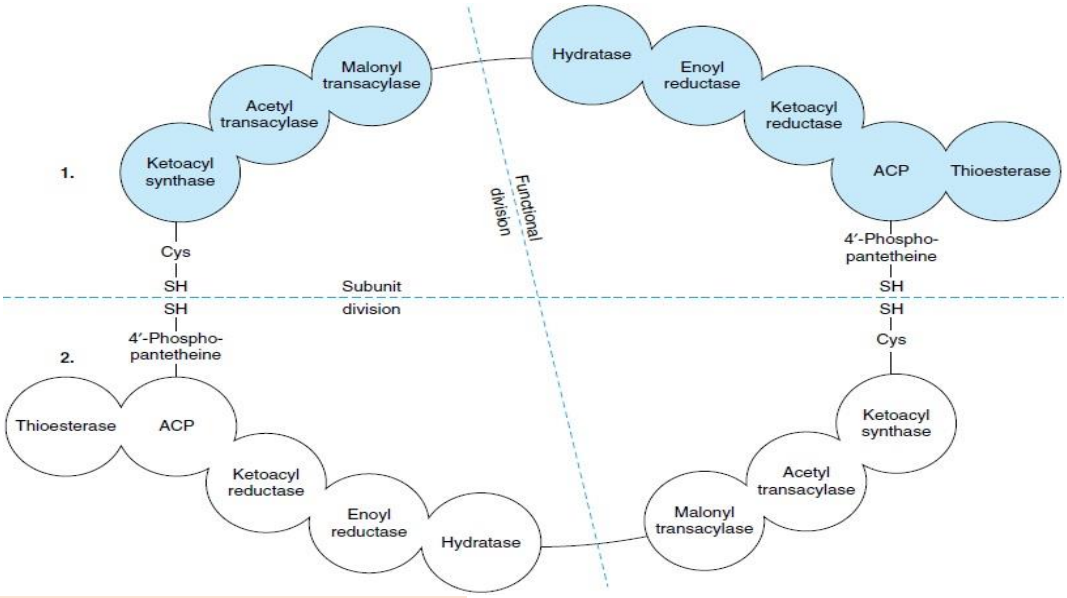
3. Fatty acid synthase complex:

a) This enzyme is a dimer i.e. formed of 2 subunits.

b) Each unit, which is called monomer, contains 7 enzymes and a terminal protein called acyl carrier protein (ACP).

c) Each monomer contains 2 -SH groups, one provided by **phosphopantotheine** and attached to ACP. The other is provided by **cysteine** and attached to the enzyme 3-ketoacyl synthase.

d) The 2 monomers are arranged head to tail, so the -SH group of ACP of one monomer is very close to the - SH group provided by 3-ketoacyl synthase of the other monomer.



REGULATION OF FATTY ACID SYNTHESIS

The key enzyme of cytoplasmic pathway is acetyl CoA carboxylase enzyme.

1- Insulin: Stimulates fatty acid synthesis through:

a) Insulin activates both acetyl CoA carboxylase and pyruvate dehydrogenase [PDH]

b) Insulin stimulates also the transport of glucose into cells.

c) Insulin inhibits Lipolysis.

2- Glucagon and epinephrine: Inhibits fatty acid synthesis through cyclic AMP

- and it also stimulates Lipolysis

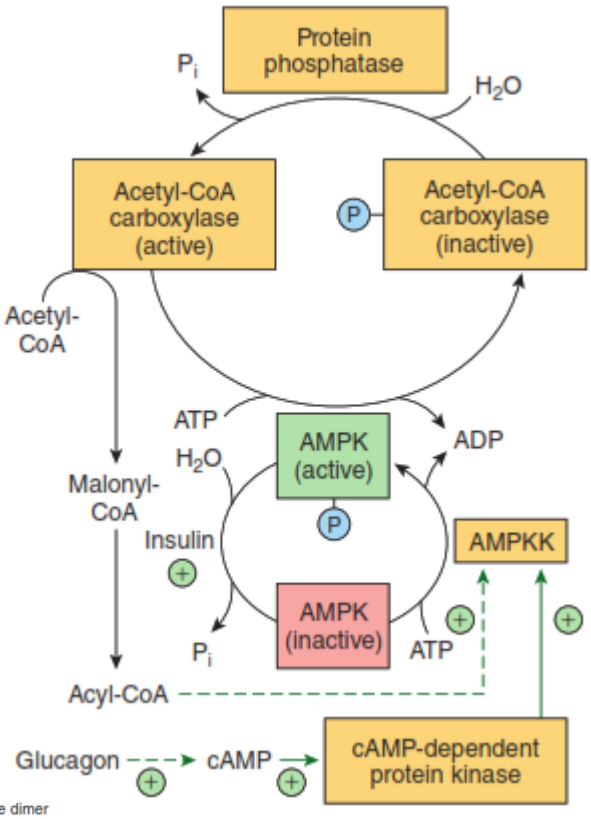
3- Long chain acyl CoA: Inhibits Fatty acid synthesis through:

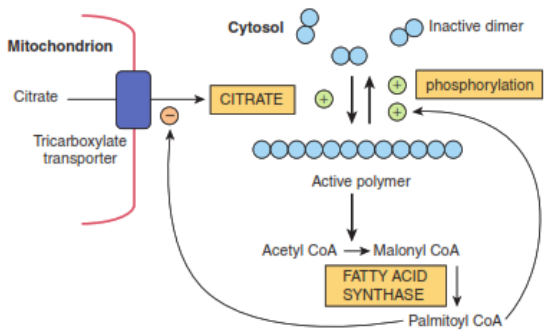
a) It inhibits allosterically acetyl CoA carboxylase.

b) It inhibits transport of citrate from mitochondria to cytosol.

c) It inhibits pyruvate dehydrogenase (PDH).

4- Citrate: stimulates fatty acid synthesis through stimulation of acetyl CoA carboxylase.





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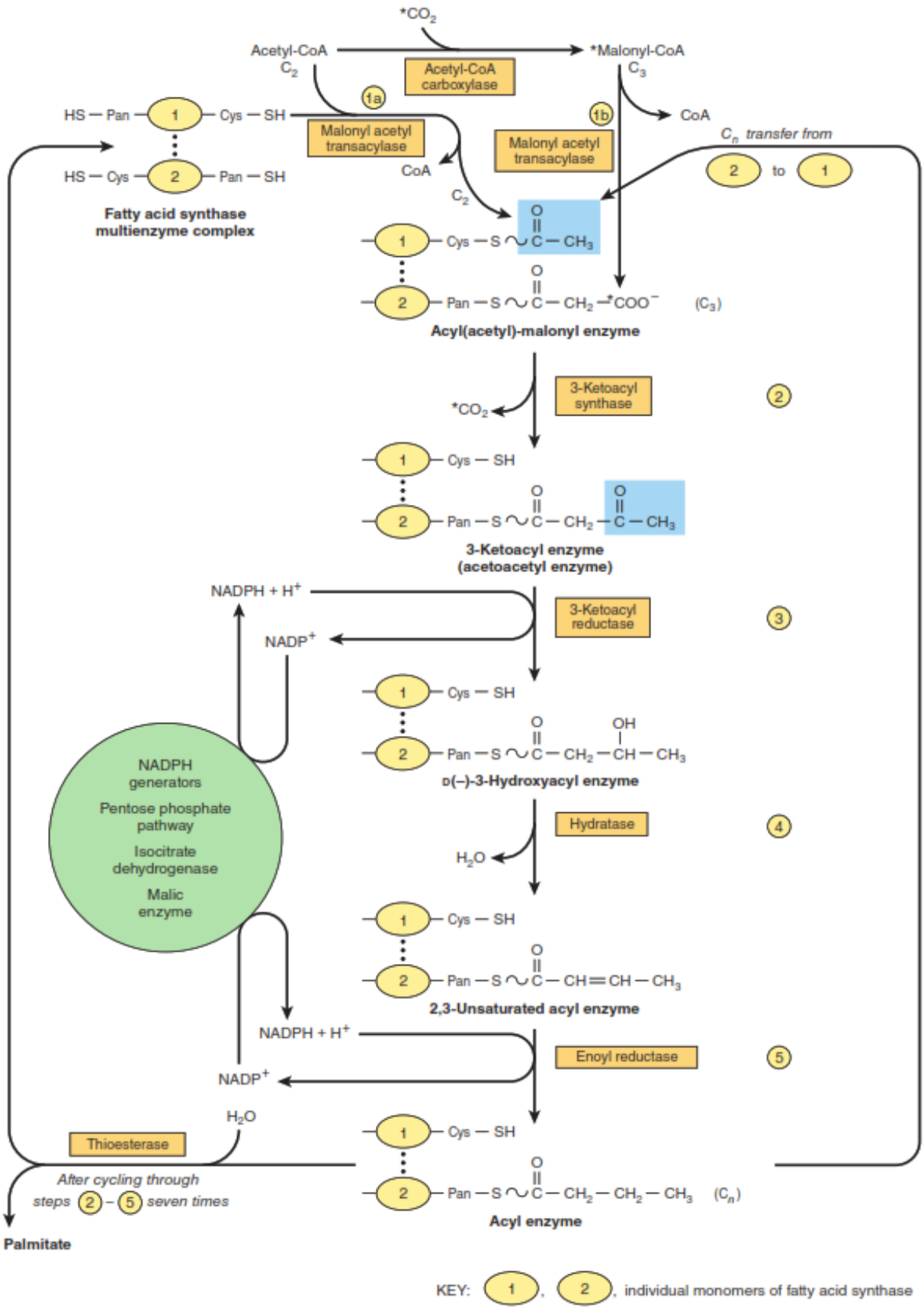
STEPS OF CYTOPLASMIC PATHWAY

- **Carboxylation of acetyl CoA to form malonyl CoA:** (committed step in the pathway).

a) Malonyl CoA is synthesized from acetyl CoA by acetyl CoA carboxylase in the presence of biotin and ATP.



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	F.A synthesis	F.A oxidation
Organ location	Mainly liver	Mainly liver and muscles
Intracellular location	Cytosol	Mitochondria
Nutritional state	After meals	Fasting
Hormonal stimulation	Insulin	Glucagon
Carrier of acetyl acyl group between cytosol and mitochondria	Citrate (mitochondria to cytosol).	Carnitin (cytosol to mitochondria)
Active carriers	> Acyl carrier protein > CoASH	> CoASH
Coenzyme	$NADP^+$	NAD^+
Two carbon donor	Malonyl CoA	Acetyl CoA
Activator	Citrate	
Inhibitor	Fatty acyl CoA (inhibits acetyl CoA carboxylase)	Malonyl CoA (inhibits Carnitine acyl transferase)
Product of pathway	Palmitate	Acetyl CoA

MICROSOMAL PATHWAY FOR F.A. SYNTHESIS

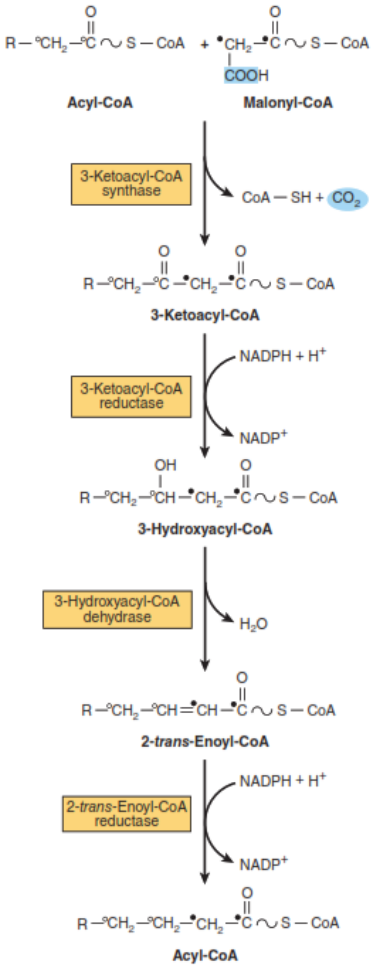
- This is probably the main site for the **elongation** of existing long chain fatty acid molecules i.e. production of fatty acids longer than 16 carbon atoms.

A. The elongated molecules (C10-C16) are derived from:

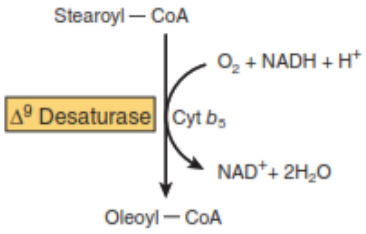
1. **Palmitate:** by cytoplasmic pathway.
2. **Fatty acids of diet.**

B. The microsomal pathway needs malonyl CoA as acetyl donor and $NADPH+H^+$ as coenzyme.

C. Function: This system becomes active during **myelination** of nerves in order to provide C22 and C24 fatty acids which are present in sphingolipids.



SYNTHESIS OF UNSATURATED F.A



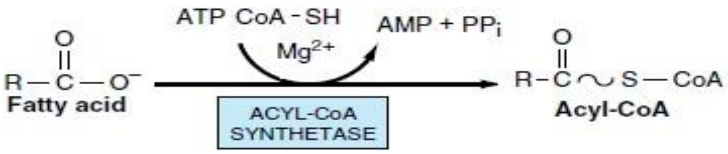
Lipogenesis

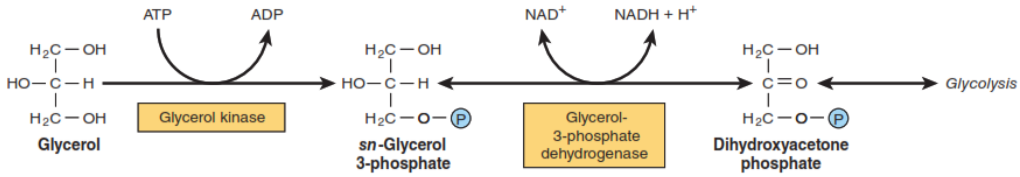
DEFINITION

synthesis of triacylglycerols from fatty acids (acyl CoA) and glycerol (glycerol-3-phosphate).

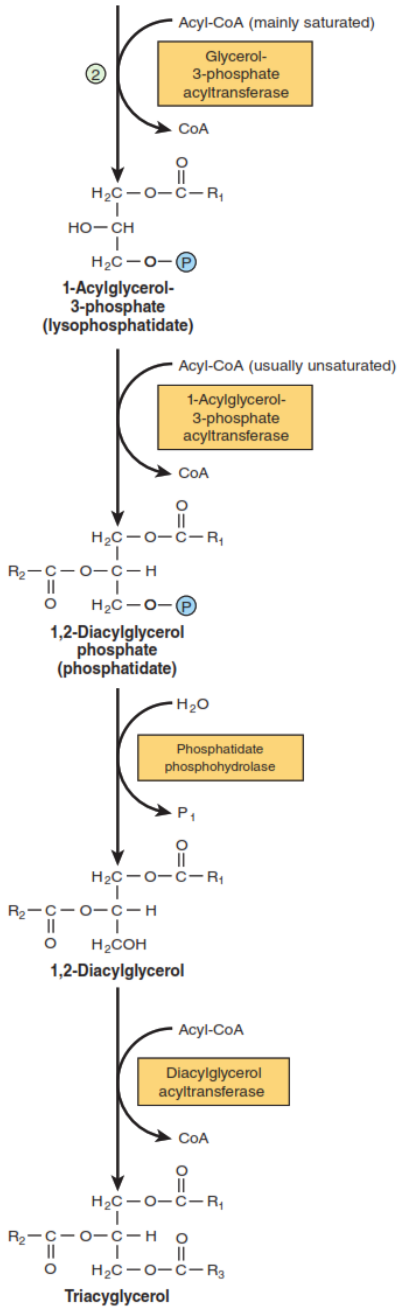
STEPS

1. Activation of fatty acids into fatty acyl CoA





2. Synthesis of glycerol phosphate
   a) In liver, kidney, intestine, and lactating mammary glands: Glycerol phosphate is formed from Glycerol by glycerokinase or from glucose through glycolysis.
   b) In muscles and adipose tissue: glycerokinase is deficient. In these tissues glycerol phosphate is formed from glucose (through glycolysis).
3. Synthesis of triacylglycerol: by reaction between acyl CoA and glycerol phosphate.



REGULATION OF LIPOGENESIS

1. After meal, lipogenesis is stimulated: Insulin is secreted which stimulates glycolysis. Glycolysis supplies dihydroxyacetone phosphate that converted into glycerol phosphate in adipose tissue.
2. During fasting lipogenesis inhibited: as anti-insulin hormones e.g. glucagon is secreted. These inhibit lipogenesis and stimulate Lipolysis.

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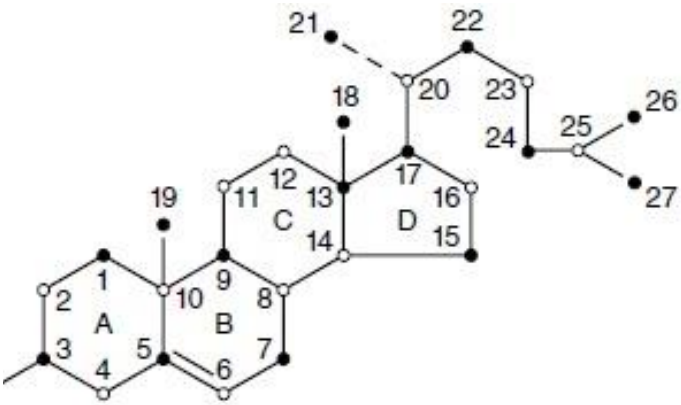
METABOLISM OF CHOLESTEROL

STRUCTURE

- Cholesterol is an animal sterol.
- It is a solid alcohol having group at C_3



SOURCES OF CHOLESTEROL

A. Endogenous: Cholesterol is formed in the body almost in all nucleated cells from Acetyl-COA (about 700 mg/day).

B. Exogenous: Cholesterol occurs only in food of animal origin such as egg yolk, meat, liver and brain. Diet supplies about 400 mg/day.

SYNTHESIS OF CHOLESTEROL

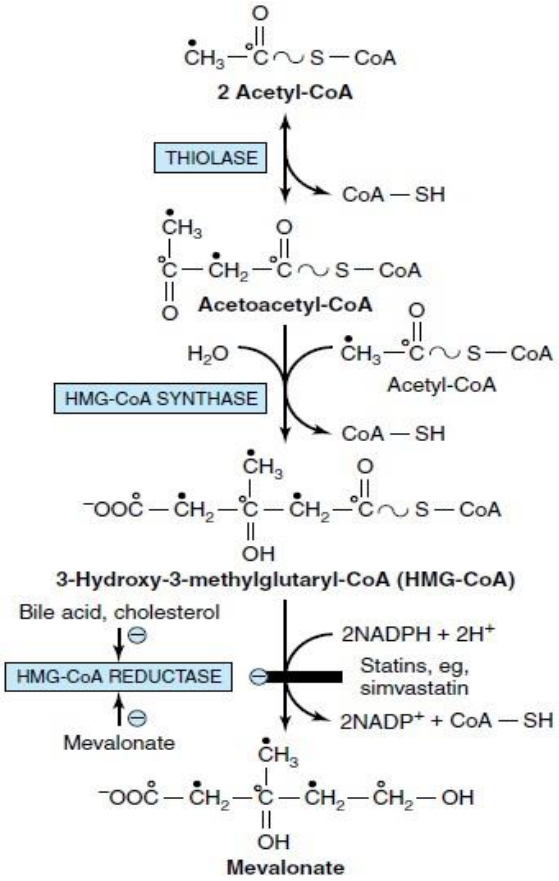
A. Location:

1. Intracellular location: Cytosol.
2. Organ location: a) Liver is the major
   b) Other tissues e.g. intestine, adrenal cortex, gonads and skin.

B. Precursor: Acetyl CoA.

C. Steps:

1. Formation of acetoacetyl CoA: by condensation of two molecules acetyl CoA:
2. Conversion of acetoacetyl CoA to mevalonate
3. Conversion of mevalonate to cholesterol.



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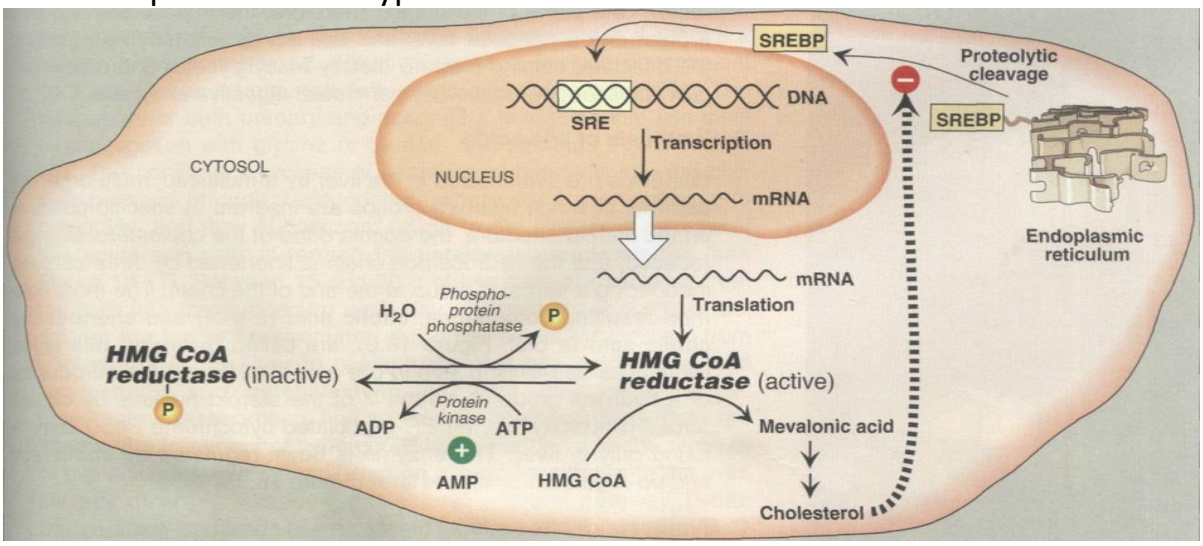
REGULATION OF CHOLESTEROL SYNTHESIS

HMG COA reductase the key enzymes for cholesterol synthesis. It is present in two forms: **active dephosphorylated** and **inactive Phosphorylated**. It is Regulated through:

1. Feedback inhibition: Cholesterol acts as feedback inhibitor of HMG COA reductase enzyme. Thus, it decreases more cholesterol synthesis.
2. Feedback regulation: Cholesterol (either synthesized by the cell or reaching it from diet) inhibits HMG COA reductase gene. this **decreases** transcription and synthesis of HMG CoA reductase.
3. Hormonal regulation:
   a) Glucagon: Inhibits HMG CoA reductase.
   b) Insulin: Stimulates HMG CoA reductase.
4. Inhibition by drugs:
   Lovastatin and **mevastatin** are drugs, which inhibit HMG CoA reductase by reversible competitive inhibition. They are used to decrease plasma cholesterol levels in patients with hypercholesterolemia.



FUNCTIONS OF CHOLESTEROL

it is important for:

1. **It enters in the structure of everybody cell particularly:**
   a) Cell membranes.
   b) In nervous tissue.
2. **Synthesis of steroid hormones.**
3. **Synthesis of bile salts.**
4. **Synthesis of vitamin D3.**

EXCRETION

- **One** gram daily → - ½ as such with bile. - ½ converted to bile.
- Some cholesterol is synthesized by intestinal cells and modified by bacteria before excretion. Bacterial enzymes reduce cholesterol into **coprostanol**, excreted in feces

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PLASMA CHOLESTEROL

A. Cholesterol present in plasma is either free or esterified (cholesteryl ester).

1. **Total** plasma cholesterol: 140 —220 mg/dl.
2. **Free** plasma cholesterol: 26 — 126 mg/dl.

Hypercholesterolemia	Hypocholesterolemia
Definition: It is increased plasma cholesterol concentration above 220 mg/dl.	**Definition:** It is decreased plasma cholesterol concentration below 140 mg/dl
- Diet rich in carbohydrate, cholesterol - diabetes mellitus - Obesity - Kidney affection (nephrotic syndrome) - Hypothyroidism as thyroxin stimulates conversion of cholesterol to bile acids. - Obstructive jaundice - familial Hypercholesterolemia	- Fasting → ↓ insulin - Unsaturated fatty acid diet - Liver diseases. - Hyperthyroidism - Chronic infection

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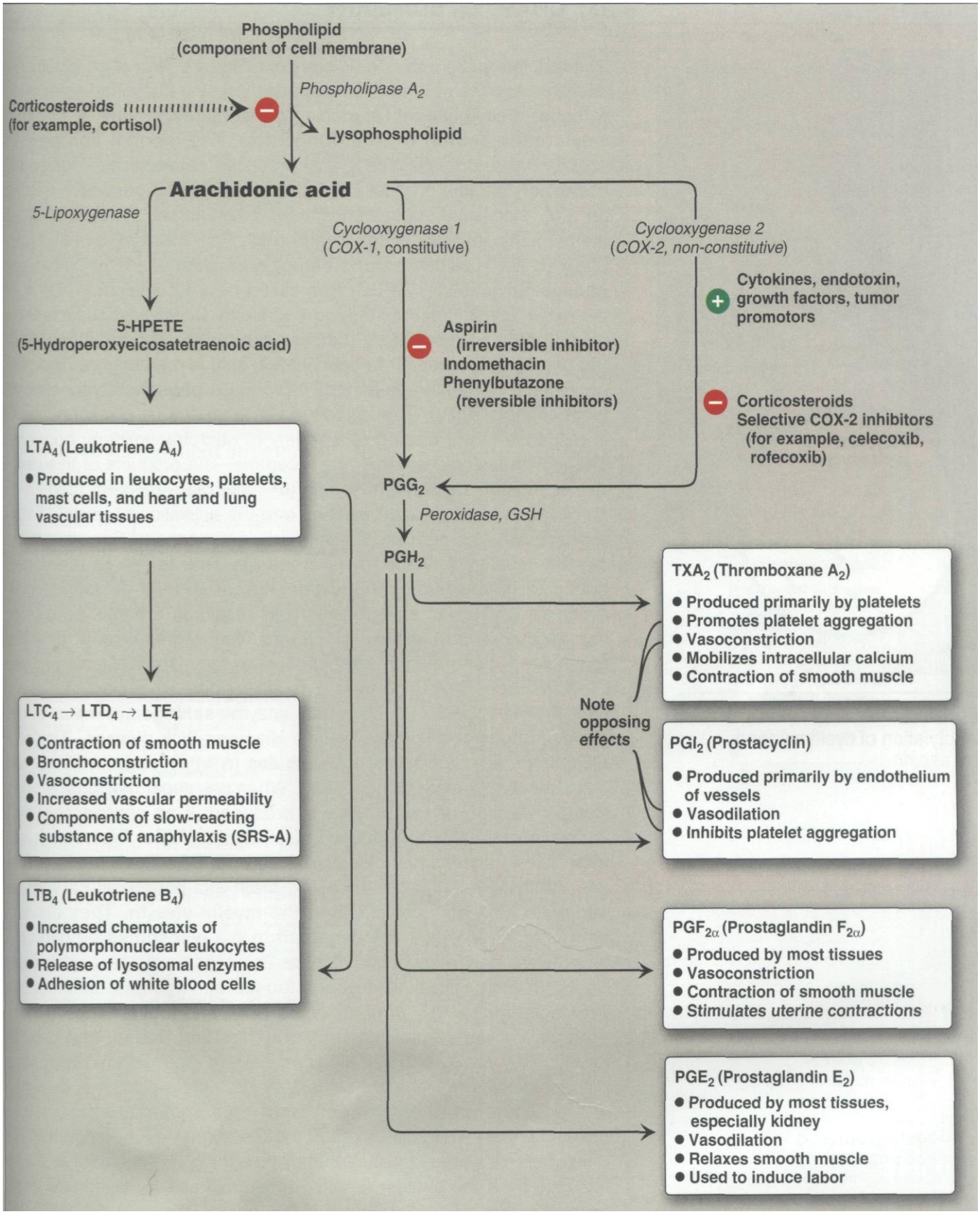
EICOSANOIDS



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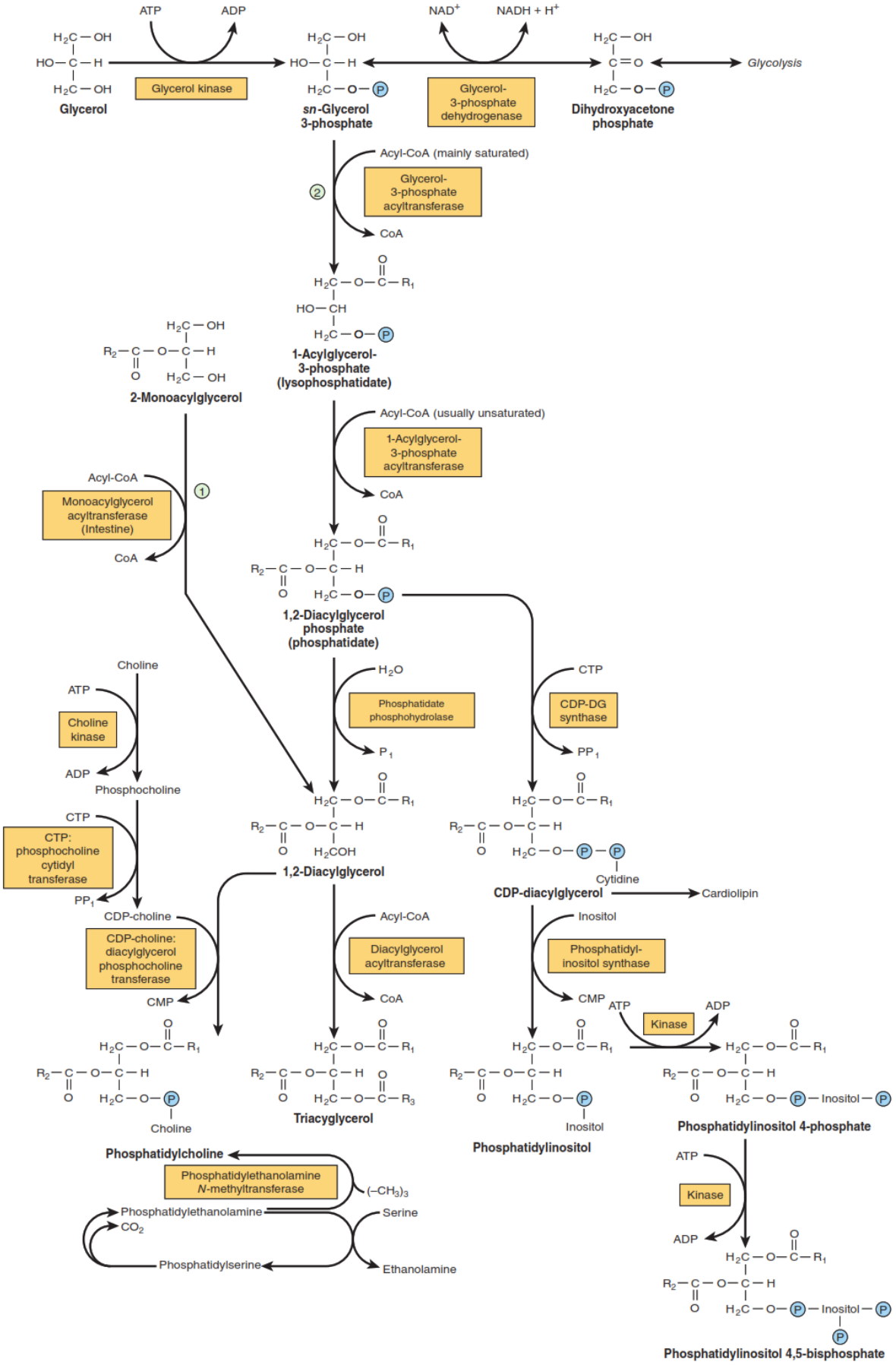
METABOLISM OF CONJUGATED LIPIDS

SYNTHESIS OF GLYCEROL PHOSPHOLIPIDS



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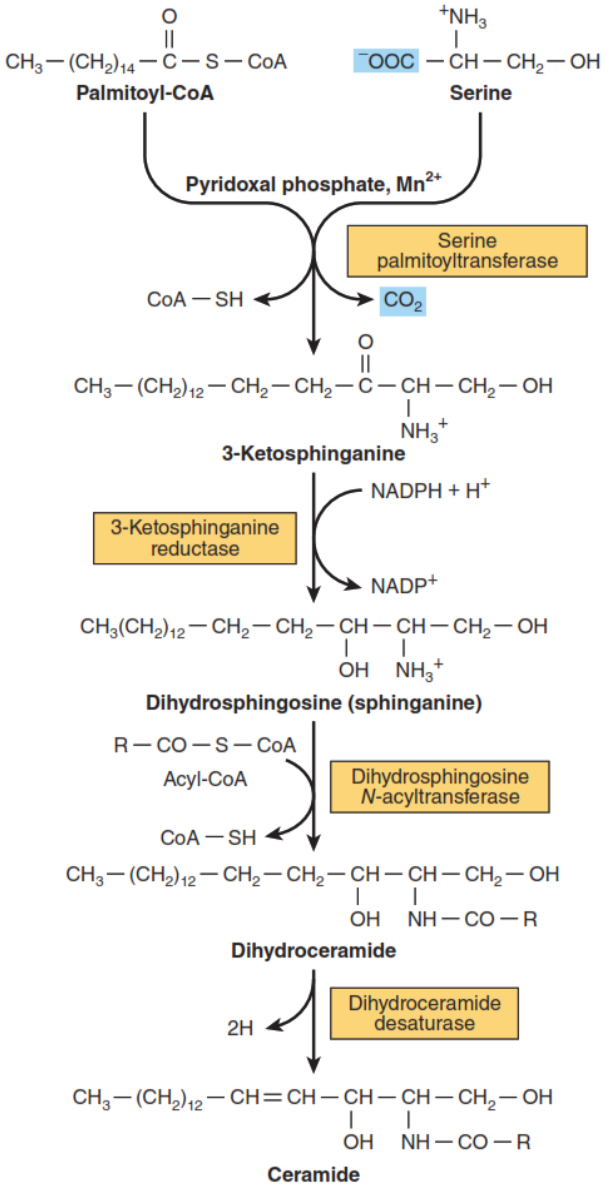
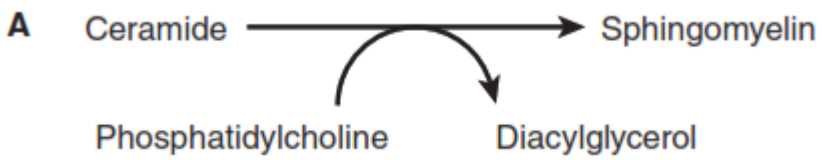
SYNTHESIS OF SPHINGOPHOSPHOLIPIDS





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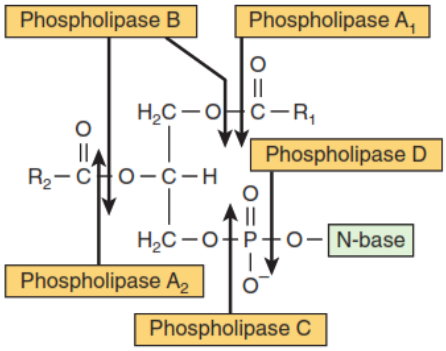
Degradation of phospholipids

- **Phosphoglycerides** are degraded by Phospholipases A1, A2, C and D.



- **Sphingomyelin** is degraded by lysosomal enzymes, sphingomyelinase its deficiency leads to a disease called Niemann Pick disease.
  - It is characterized by **enlarged liver and spleen** and **death at early life**
- **Plasma enzyme called LCAT** (lecithin cholesterol acyl transferase) can act upon second fatty acyl CoA of converting it into lysolecithin.

Lecithin + Cholesterol $\xrightarrow{\text{LCAT}}$ **Cholesterol ester + lysolecithin**

FUNCTIONS OF PHOSPHOLIPIDS

- Phospholipids enter in the structure of cell membrane.
- Phospholipids containing Choline (e.g. lecithin) act as neurotransmitters. They also act as methyl donors in transmethylation reaction.
- Phospholipids act as **lipotropic factors** i.e. prevent accumulation of fat in liver and hence prevent fatty liver.
- Dipalmityl lecithin acts as **surfactant** in the lungs. It prevents adherence of alveolar wall. Its deficiency leads to respiratory distress syndrome in premature babies
- Cephalin has a role in **coagulation** mechanism.
- Lipositol (Phosphatidyl Inositol) acts as precursor for **Inositol triphosphate**. That acts as **2nd messenger**, mediating action of some hormones inside target cells.
- Phospholipids in bile make cholesterol **soluble**. Their deficiency leads to cholesterol gallstones.

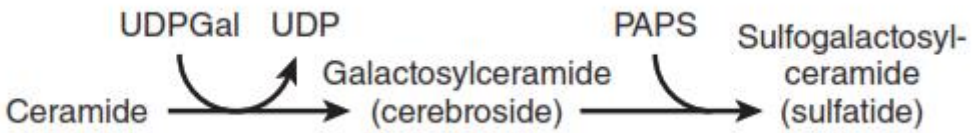
METABOLISM OF GLYCOLIPIDS (SPHINGOLIPIDS):

- Glycolipids are lipid containing carbohydrates
- They also contain sphingosine and one fatty acid. They differ from each other according to the type of carbohydrate content.

SYNTHESIS OF CEREBROSIDES

They Contain galactose.

1. Synthesis of sphingosine 2. Formation of ceramide. 3. Activation of galactose



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DEGRADATION OF CEREBROSIDES

is by glucocerebrosidase its deficiency leads to a disease called Gaucher's disease.

- It is characterized by **mental retardation** and **enlarged liver and spleen** in children,

LIPIDOSIS:

- Errors of phospholipids and sphingolipids metabolism:
- These are a group of diseases in which there is abnormal accumulation of Phospholipids and glycolipids in nervous tissue. They are common in children.

They are characterized by:

1. Deficiency of specific lysosomal enzymes responsible for degradation of sphingolipids
2. Accumulation of sphingolipids in tissues leads to their enlargement e.g. liver and spleen enlargement
3. Mental retardation is present in many diseases
4. The most common diseases are Gaucher's disease and Niemann Pick diseases.

Disease	Enzyme Deficiency	Lipid Accumulating[1]	Clinical Symptoms
Tay-Sachs disease	Hexosaminidase A	Cer—Glc—Gal(NeuAc)÷GalNAc G_{M2} Ganglioside	Mental retardation, blindness, muscular weakness.
Fabry's disease	α-Galactosidase	Cer—Glc—Gal÷Gal Globotriaosylceramide	Skin rash, kidney failure (full symptoms only in males; X-linked recessive).
Metachromatic leukodystrophy	Arylsulfatase A	Cer—Gal÷OSO_3 3-Sulfogalactosylceramide	Mental retardation and psychologic disturbances in adults; demyelination.
Krabbe's disease	β-Galactosidase	Cer÷Gal Galactosylceramide	Mental retardation; myelin almost absent.
Gaucher's disease	β-Glucosidase	Cer÷Glc Glucosylceramide	Enlarged liver and spleen, erosion of long bones, mental retardation in infants.
Niemann-Pick disease	Sphingomyelinase	Cer÷P—choline Sphingomyelin	Enlarged liver and spleen, mental retardation; fatal in early life.
Farber's disease	Ceramidase	Acyl÷Sphingosine Ceramide	Hoarseness, dermatitis, skeletal deformation, mental retardation; fatal in early life.

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LIPOPROTEINS

CHYLOMICRONS METABOLISM

1-Site of synthesis: intestinal mucosal cells

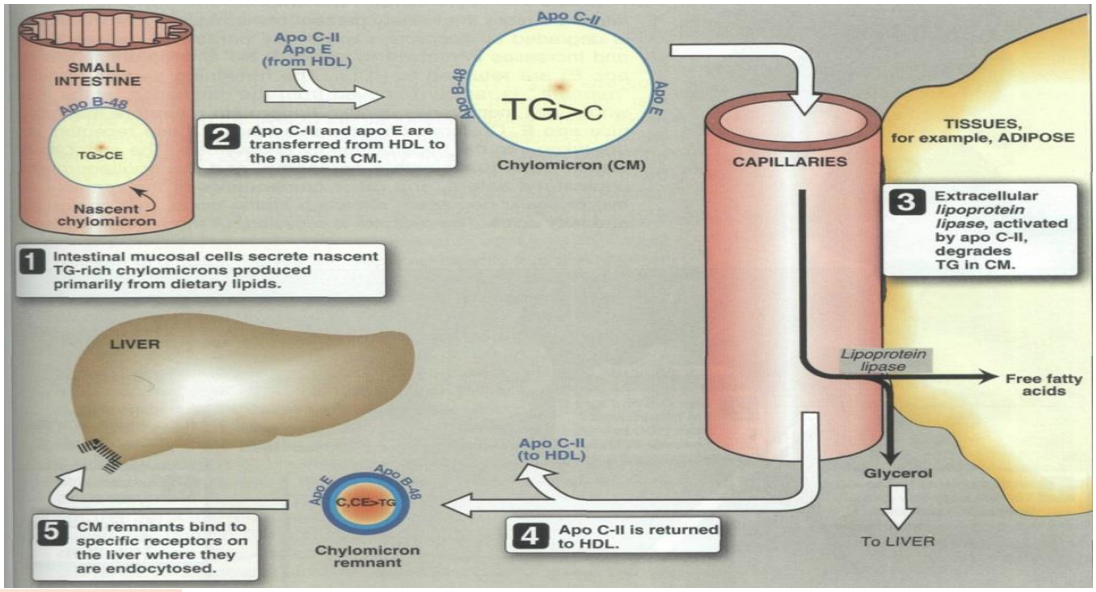
2-Functions: transport dietary lipids from intestine to peripheral tissues.

3-Structure:

a- Main lipids: triacylglycerols. Chylomicrons contain also cholesterol, phospholipids and fat soluble vitamins.

b- Proteins: (2%), apo B_{48} and receives apo CII and apo E from **HDL**.

4-catabolism: TG are hydrolyzed by lipoprotein lipase (which is activated by apo CII). The remaining parts are **chylomicron remnants**, which are then taken up by the liver. Hepatocyte receptors can recognize apo B_{48} and apo E.



VLDL METABOLISM

1- Site of synthesis: Liver.

2- Functions: transport lipids mainly TG from liver to peripheral tissues.

3- Structure:

a- Main lipids: triacylglycerols. It contains also cholesterol, phospholipids.

b- Proteins: (12%), apo B_{100} and receives apo CII and apo E from **HDL**.

5- **Catabolism:** TG are hydrolyzed by lipoprotein lipase (that is activated by apo CII). The remaining parts are IDL, which are then converted into LDL by transferring phospholipids, apo CII and apo E to HDL.

LDL METABOLISM

1-SITE OF SYNTHESIS: circulation from VLDL.

2-FUNCTION: LDL particles provide cholesterol to peripheral tissues.

3-STRUCTURE:

a- Lipid contents: cholesterol, cholesterol esters and phospholipids.

b- Protein contents: (22%), apo B_{100}

4-CATABOLISM:

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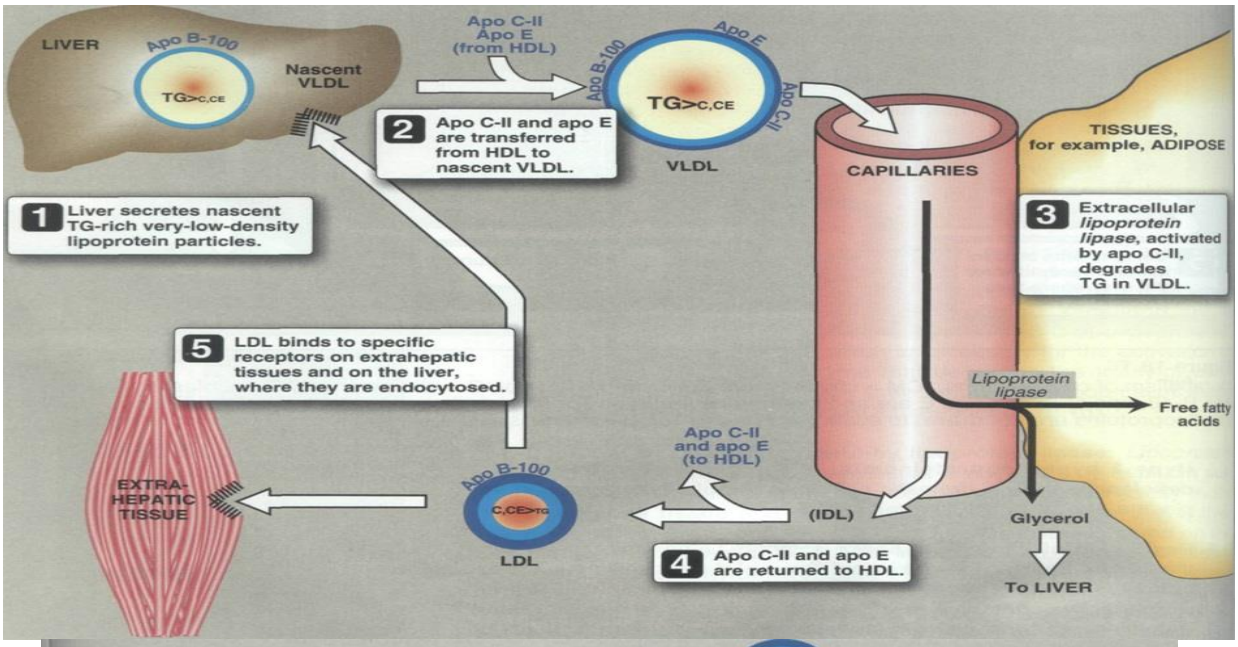
LDL apo B_{100} are recognized by tissue receptors. After binding with receptors, the LDL are internalized by endocytosis. Inside cells LDL are separated from receptors and hydrolyzed by lysosomal enzymes releasing cholesterol, amino acids, fatty acids and phospholipids.

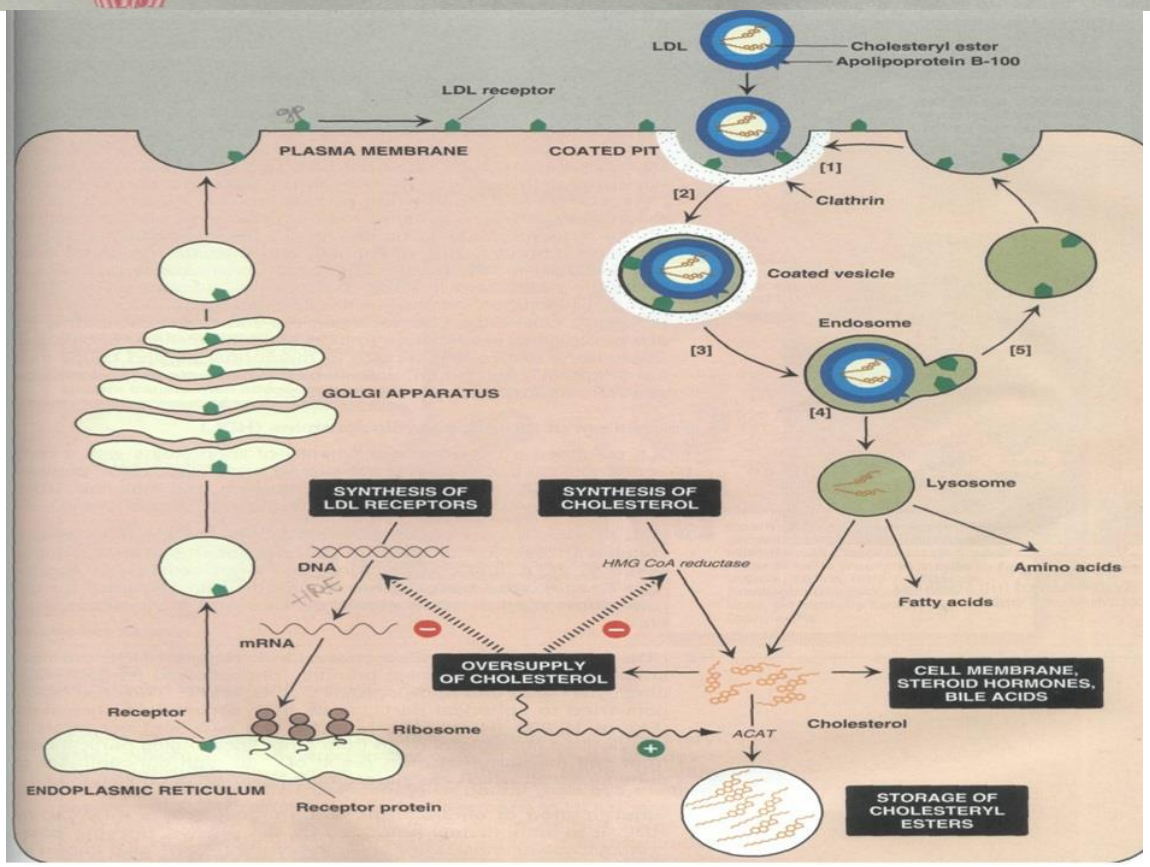
***If the cell contains oversupply of cholesterol from LDL, HDL or chylomicron remnants, the cholesterol amount can be decreased by:**

a- Inhibition of HMG-CoA reductase → Inhibition of cholesterol synthesis.

b- Stimulation of **ACAT** enzyme → Cholesterol ester.

c- Inhibition of synthesis of **LDL receptors** → inhibition of LDL uptake by cells





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HDL METABOLISM

1-Site of HDL synthesis: Liver.

2-Functions:

a- Contain Apo CII, which activates **lipoprotein lipase** that hydrolyzes TG.

b- Remove cholesterol from peripheral tissues and esterified it by **LCAT** enzyme → Cholesterol esters.

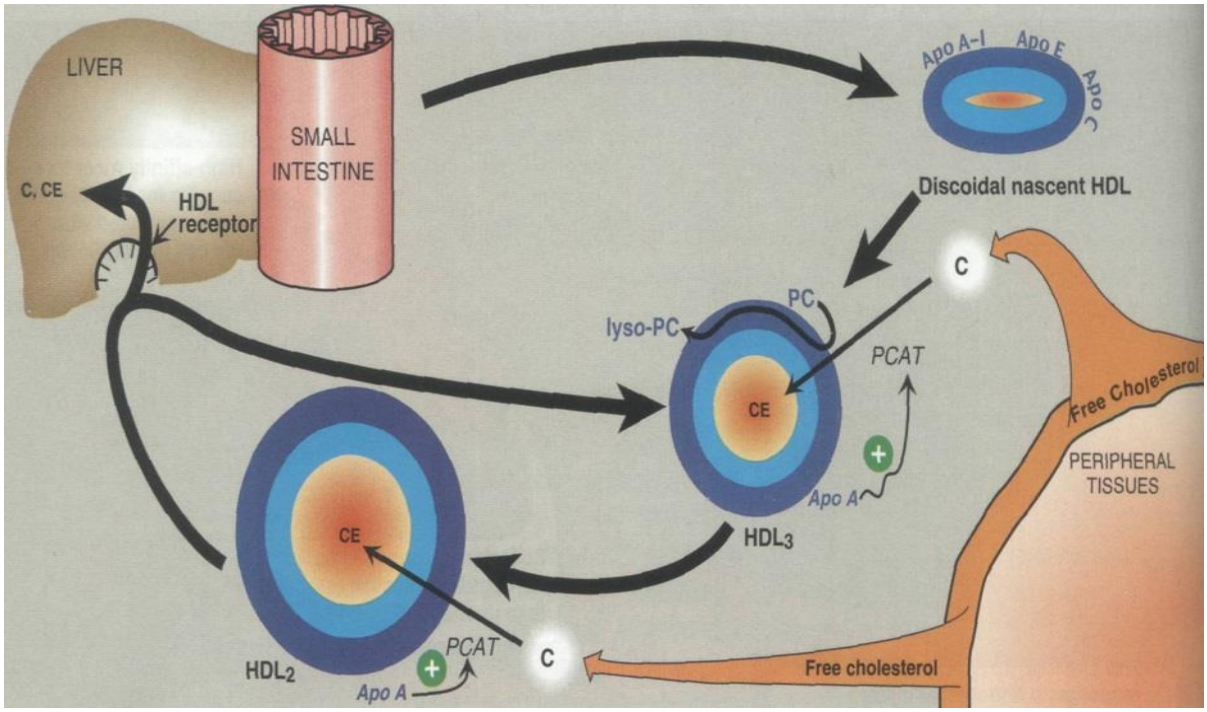
c- Carry cholesterol esters to VLDL & chylomicrons to the liver.

3-Structure:

a- Main lipids: cholesterol (free and esterified) and phospholipids, mainly lecithin.

b- Proteins: (50%), apo A-1 (which activates **LCAT**), apo CII (which activates **lipoprotein lipase** and E (which is recognized by hepatic receptors)

4-Catabolism: HDL accepts unesterified cholesterol from peripheral tissues. Then HDL particles (by **LCAT** enzyme) esterify cholesterol into cholesterol esters. Then HDL is taken up by the liver cells where Cholesterol esters are released inside them to be utilized in the formation of lipoproteins or excreted in bile.



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APOPROTEINS (APOLIPOPROTEINS)

- **Definition:** These are proteins (globulins) present in association with plasma lipids to form lipoproteins.
- **Functions**:
  1. Apolipoproteins form with lipids water-soluble compounds, so they help transport of lipids between tissues.
  2. Some apoproteins activate certain enzymes e.g. ***Apo C II*** activates lipoprotein lipase and ***Apo-A1*** activates LCAT.
  3. They act as liganda (connection) for interaction of lipoprotein with their receptors in tissues i.e. receptors of lipoproteins in tissues can recognize lipoproteins through their apoproteins e.g. apo B100 for LDL receptors

Classification

	LIPOPROTEIIIS	COMMEIIT
Apo A-I	HD L	*Activator of LCAT *Legend for HDL-receptors
Ape B- 100	LDL-YLDL-IDL	*synthesized by liver *Legend for LDL-receptcrs
Ape B- 48	Chylomicrons - chylomicron remnants	*Synthesized by intestine *Legend for chylomicron remnant receptors in Liver.
Ape C II	Chylomicrons-VLDL-HDL	Activator of lipoprotein lipase
Ape D	HDL	May act as lipid transfer protein.
Ape E	Chylomicrons - Chylomicron remnants – VLDL - HDL	* Legend for chylomicron remnant receptors in liver. * Legend for LDL receptors in tissues.

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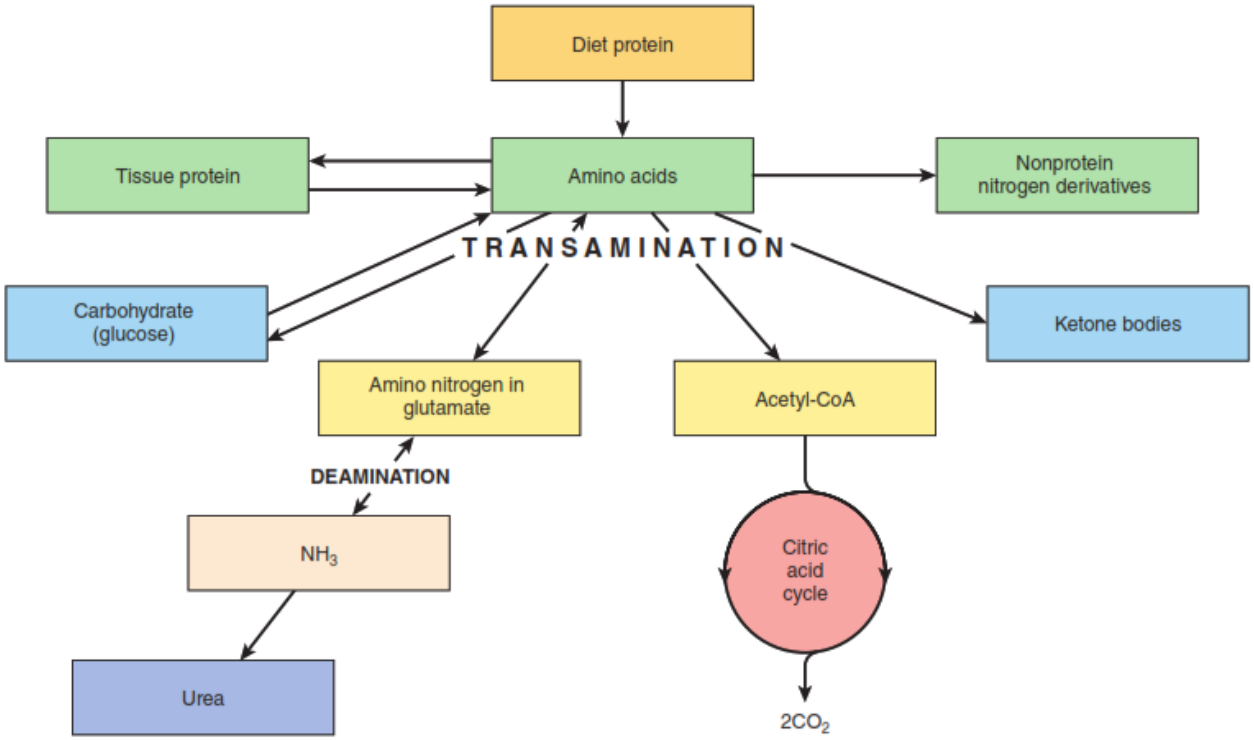
CHAPTER 7

Proteins Metabolism

CHAPTER MAP

ptn Metabolism

CATABOLIC PATHWAYS	Ammonia And Urea	Amino Acid Metabolism
1- Transamination. 2- Deamination 3- Transdeamination 4- Decarboxylation.	1- Source and fate of ammonia. 2- Ammonia intoxication 3- Urea cycle	1- Glycine 2- Phenyl alanine 3- Tyrosine 4- Tryptophan 5- Rest of A.A



GENERAL CATABOLIC PATHWAYS OF AMINO ACIDS

In human, the end products of protein and amino acids catabolism are ammonia and urea. They are produced through the following catabolic pathways.

- Transamination.
- Deamination: Oxidative - Non oxidative - Hydrolytic.
- Transdeamination: i.e. transamination followed by deamination.
- Decarboxylation.

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DEAMINATION

DEFINITION

It is the removal of amino group from amino acids in the form of ammonia (NH_3).

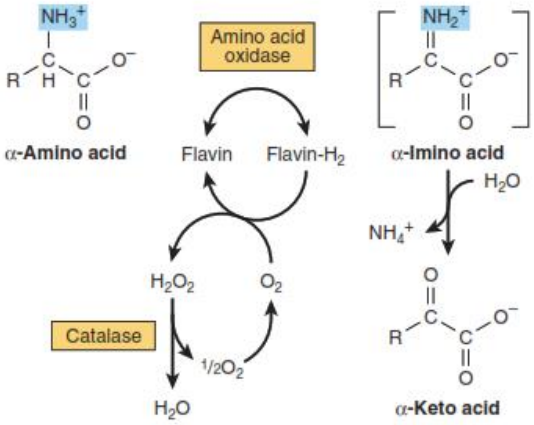
SITE

Mostly liver and kidney.

TYPES

1- Oxidative, 2-NON-Oxidative, 3-hydrolytic deamination.

1- Oxidative



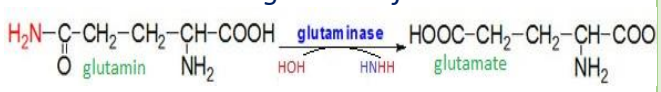
	L. a.a oxidase	D.a.a oxidase	L-glutamate dehydrogenase
Carrier	FMN	FAD	NAD or NADP.
Site	Liver & kidney	Liver & kidney	Most tissues.
Activity	Low	highly active	highly active
Reversibility	Irreversible	irreversible	Reversible

2- Non-oxidative deamination

- For **hydroxy** amino acids e.g. serine, threonine, without removal of (H^+)
- Its coenzyme is: pyridoxal phosphate (**PLP**).

3- Hydrolytic deamination

For glutamine and asparagine	For adenosine monophosphate (AMP):
- Enz → glutaminase & asparaginase *- Glutaminase is present in kidney.* *- It produces ammonia (NH_3), which is used in regulation of acid base balance*	- In **muscles**, AMP is hydrolytically deaminated into inosine monophosphate Producing (**NH_3**). This occurs by a series of reactions called: **(IMP – AMP) cycle**.



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TRANSAMINATION

DEFINITION

- It is the transfer of amino group from α-amino acid to α-ketoacid to form a new α-amino acid and a new α-ketoacid.

MECHANISM

1. By enzymes called transaminases (or amino transferases) catalyze transamination.
2. Pyridoxal phosphate (PLP = active vitamin B6) is the coenzyme of all transaminases.
3. For all amino acids except: (lysine, threonine, proline and hydroxyproline).
4. All transamination reactions are reversible.
5. Present either in cytosol or in both cytosol and mitochondria of most tissues.
6. Among all transaminases, 3 are present in most mammalian tissues and they are of clinical importance. These are: ALT, AST and glutamate transaminase.

Enzymes	Site	Function
Alanine transaminase (ALT): **or** Glutamate pyruvate transaminase (GPT).	cytosol	ALT is an enzyme that catalysis the transfer of amino group from Alanine to α-Ketoglutarate to form glutamate and pyruvate.
Alanine + α-Ketoglutarate $\xleftrightarrow{\text{ALT} \quad \text{PLP}}$ **pyruvate + glutamate**		
Aspartate transaminase (AST): **or** Glutamate oxaloacetate transaminase (GOT).	cytosol and mitochondria	catalysis the transfer of amino group from Aspartate to α-Ketoglutarate to form Glutamate and oxaloacetate.
Aspartate + α-Ketoglutarate $\xleftrightarrow{\text{AST} \quad \text{PLP}}$ **oxaloacetate + glutamate**		
Glutamate transaminase:		Catalysis the transfer of amino group from any amino acid to α-Ketoglutarate.

Role of pyridoxal phosphate in transamination

Acts as an **intermediate** carrier of amino group.

Functions of transamination

1. **Transfer** of amino group (-NH2) from most amino acids to α-Ketoglutarate to form **glutamate** then deaminated to give **ammonia**.
2. Transamination is important for formation of **non-essential amino acids**.

Diagnostic importance of transaminases (ALT and AST): normally intracellular

↑ **ALT** → liver diseases

↑ **AST** → heart muscle (myocardial infarction), skeletal muscle or kidney.

↑ **Both** → damage of liver cells with escape of hepatic enzymes into blood.

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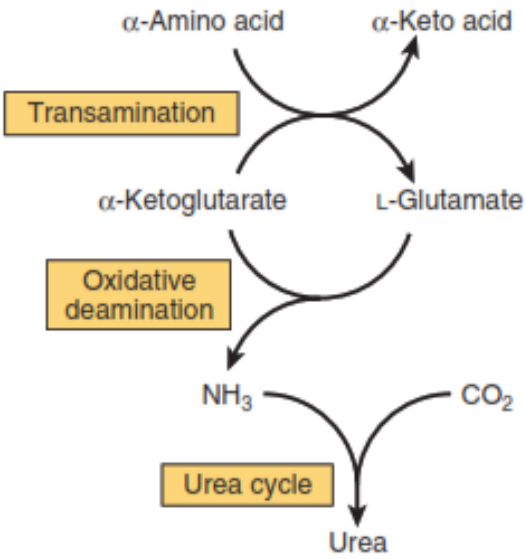
TRANSDEAMINATION

Definition:

- It is **transamination** of most amino acids with α-Ketoglutarate to form glutamate, Then glutamate is **deaminated** to give ammonia (NH_3).
- It is the main pathway by which amino group (NH_2) of most amino acids is released in the form of ammonia (NH_3).



DECARBOXYLATION

Definition:

removal of **CO_2** of amino acids produces the corresponding amines.

Functions:

- Some amines have important biologic functions: e.g.

1. Histamine (from histidine) is vasodilator.
2. γ-Amino butyric acid (from glutamate) is neurotransmitter.

Destruction of amines

- The resulting amines are further oxidized -after carrying out their functions by amine oxidase enzymes.
- Amine oxidase enzymes are two types: monoamine oxidase and diamine oxidase. Both contain **Pyridoxal phosphate** and **copper** as prosthetic groups.

e.g. ??

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AMMONIA (NH_3)

DEFINITION

- Ammonia is a toxic substance especially to the **central nervous system**.
- Any ammonia formed in the peripheral tissue must be moved to the liver to be converted into **urea**.
- This maintains ammonia at low level in circulating blood.

BLOOD AMMONIA

- Blood contains traces of ammonia: 10- 80 ug/dl.

Sources and fate of ammonia

SOURCES	FATE
1. Transdeamination of amino acids: In Many tissues, particularly liver 2- Glutamine: The kidneys form ammonia from glutamine by glutaminase enzyme. Most of this ammonia is used in regulation of Acid base balance. 3. Purines and pyrimidines metabolism. 4. Various nitrogenous compounds e.g.: monoamines that act as neurotransmitters. 5. In intestine: ammonia is produced by the action of bacterial enzymes on: a) Dietary amino acids. b) Urea secreted into the intestine.	1. Formation of non-essential amino acids: Through Transdeamination. 2. Formation of glutamine: a) Glutamine synthetase is a mitochondrial enzyme present in many tissues as kidney and brain. b) Glutamine has the following functions: 1) Regulation of acid base balance: glutamine is deaminated by glutaminase, releasing ammonia again. Ammonia is used in regulation of acid base balance by the kidneys. 2) Removes the toxic effect of ammonia In brain: Ammonia + Glutamate → Glutamine. 3) Glutamine is the source of: N_3 and N_9 of purines bases. 4) Glutamine is used in detoxication of phenyl acetic acid (a toxic substance). 3. Formation of urea: It is the main pathway by which the body can get rid of ammonia. 4. Excretion in urine

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UREA

DEFINITION

- Urea (H2N-CO-NH2) is the main end product of protein (amino acids) metabolism.
- Urea formation is the pathway through which the liver can convert toxic ammonia into non-toxic urea.

SITE OF UREA FORMATION

1. Liver is the only site for urea formation.
2. Then urea is transported in the blood to the kidney to be excreted in urine (urine urea is 20-40 g/day).

PLASMA UREA

1. Plasma urea: is 20-50 mg/dl.
2. **Diagnostic importance** of plasma urea determination:
   a) Measurement of plasma urea is one of the **kidney function tests**.
   b) In kidney diseases as in renal failure, kidney fails to excrete urea → High blood urea concentration (uremia).

UREA FORMATION

It is also called **Krebs'** Henseleit cycle.

SITE: Liver.

1. The first two reactions occur in mitochondria where other reactions occur in cytosol.
2. **Six amino acids share in urea cycle**: ornithine, citrulline, arginosuccinate, Aspartate. And Arginine. The **6th** one is **N-acetyl glutamate** that acts as allosteric activator of Carbamoyl phosphate synthase I.

STEPS

1. Formation of Carbamoyl phosphate:

a) This reaction occurs in mitochondria.

b) It needs **CO_2** (a product of citric acid cycle), ammonia (a product of deamination of glutamate) and phosphate (from ATP).

c) This reaction is catalyzed by **Carbamoyl phosphate synthase I.** It needs magnesium (Mg) ions, manganese (Mn^{++}) and N-acetyl glutamate as activators.

d) 2 ATP molecules are used in this reaction, one to provide phosphate and the other to supply energy.

2. Formation of citrulline:

a) This reaction also occurs in mitochondria.

b) Carbamoyl phosphate reacts with **ornithine**, in the presence of ornithine **transcarbamoylase** enzyme producing citrulline.

c) Citrulline then passes to **cytosol.**

d) Ornithine is regenerated with each turn of urea cycle**.**

3. Formation of arginosuccinate:

a) Citrulline reacts with **Aspartate** in the **cytosol** to form **arginosuccinate.**

4. Cleavage of arginosuccinate:

a) It is cleaved into **Arginine** and **Fumarate.**

5. Cleavage of Arginine into ornithine and urea:

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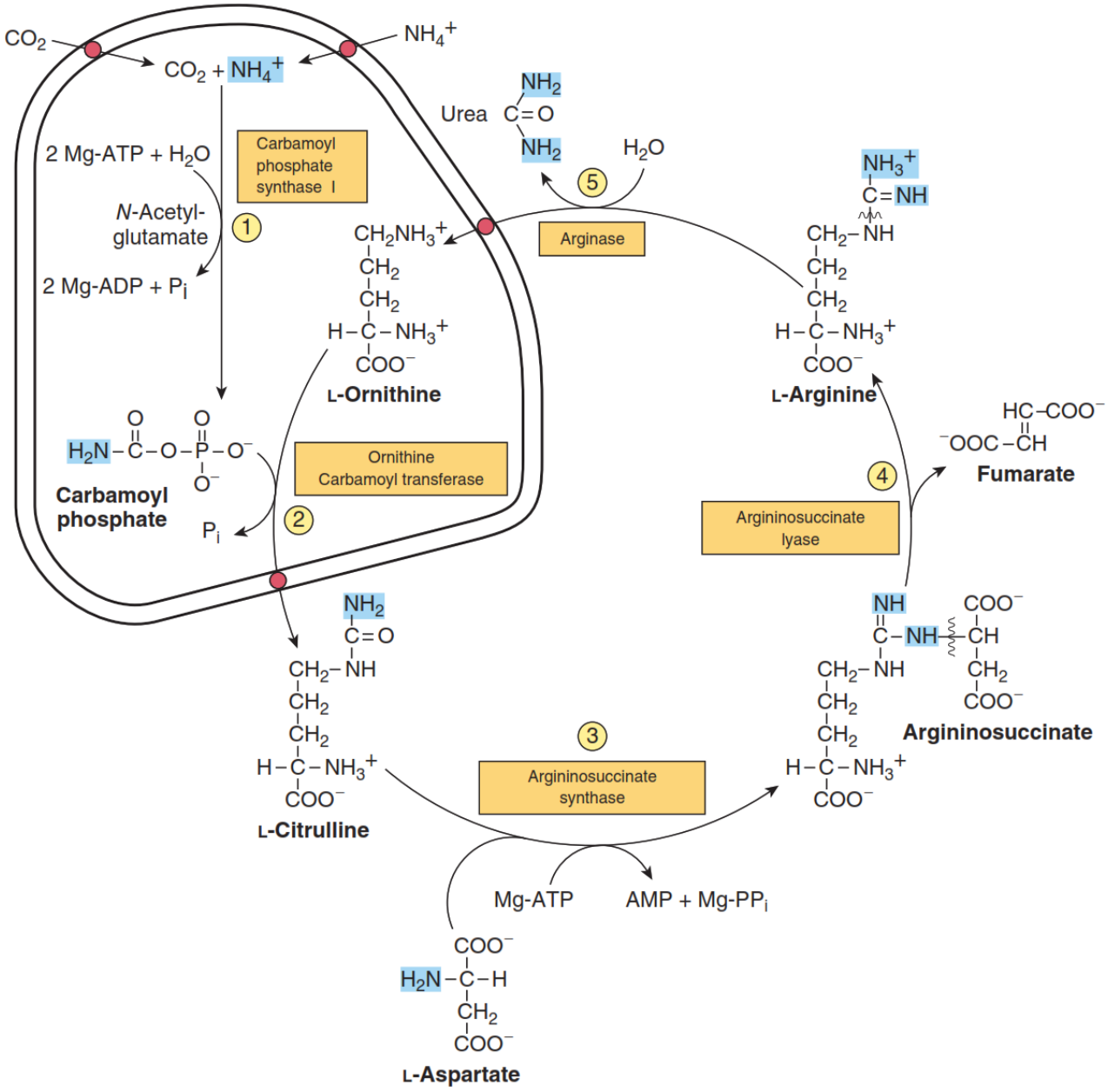
a) Ornithine then passes to the **mitochondria** to start a new cycle**.**

b) Urea passes to the blood to be excreted by the kidney in urine**.**



- **Three ATP molecules** and **four high-energy phosphate bonds** are utilized in the reactions.
- **Sources of different atoms of urea (H_2N-CO-NH_2):**
  1. **1st Nitrogen atom:** from ammonia.
  2. **Carbon atom:** from CO_2.
  3. **2nd Nitrogen atom:** from Aspartate.

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AMMONIA INTOXICATION

Definition: Excess ammonia which is toxic to the central nervous system.

Symptoms: Include:

A. Flapping tremors, slurring speech, blurring vision and vomiting in infancy.

B. High concentration of ammonia may cause **coma** and **death**.

Types and causes of hyperammonemia

Acquired hyperammonemia

1- **Liver cell failure**: The diseased liver cells cannot convert ammonia into urea.
2- **Renal failure**
3- **Shunt operation** between portal and systemic circulation.
4- **Collaterals** between portal and systemic circulation due cirrhosis of liver by bilharziasis , hepatitis etc.

Inherited hyperammonemia

Result from genetic deficiency of one of five enzymes of urea cycle → Failure to synthesize urea → Hyperammonemia during the first week after birth → Mental retardation.

Type I	Car. Ph. synthetase I.
Type II	Transcarbamoylase.
Ctrullinemia	Arg.succ.synthetase
Argininosuccinuria	Arginosuccinase
Argininemia	Arginase

Mechanism of ammonia intoxication:

- At normal blood ammonia level, any ammonia reaches the brain incorporated into glutamine formation by glutamine synthetase enzyme.
- In cases of hyperammonemia, ammonia reacts not only with glutamate, but also with **α-Ketoglutarate** by **glutamate dehydrogenase** enzyme. This depletes **α-Ketoglutarate** which is an essential intermediate of citric acid cycle → Decrease in **ATP** and **energy** production → symptoms of ammonia intoxication → **coma**.

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FATE OF α -KETO-ACIDS

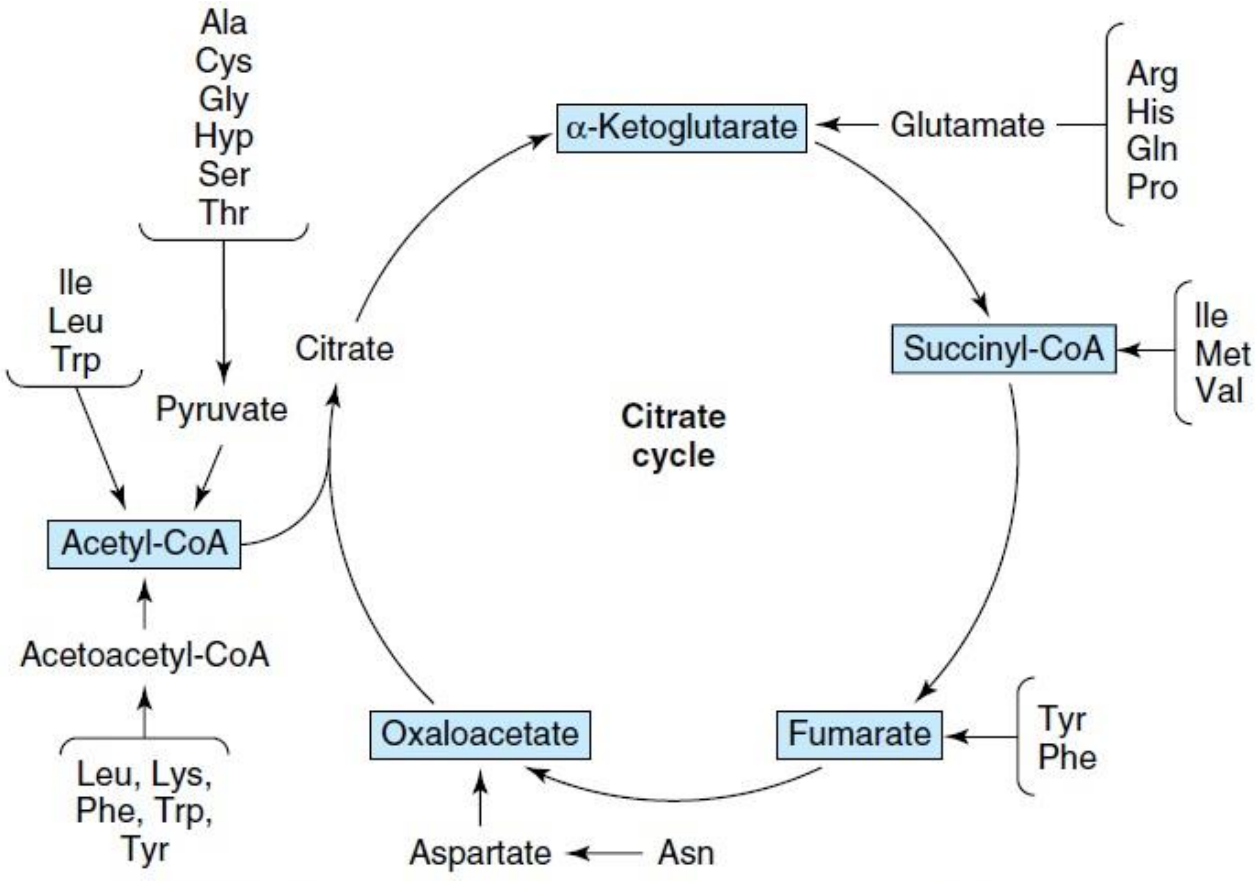
- The α-ketoacid (the carbon skeleton) remaining after the removal of the amino group **(NH_2)** by transamination and deamination of amino acids may undergo:

A. Reamination: by ammonia (**NH_3**) to form again the corresponding amino acid (by **glutamate dehydrogenase**).

B. Catabolized to form seven products: pyruvate, acetyl CoA, acetoacetyl CoA, Fumarate, oxaloacetate, α-Ketoglutarate and Succinyl CoA.

C. These products enter different pathways which lead to:

1. Synthesis of **glycogen** or **glucose.**
2. Synthesis of **lipids.**
3. Complete oxidation into **CO_2** and **H_2O**.



Amphibolic intermediates formed from the carbon skeletons of amino acids.

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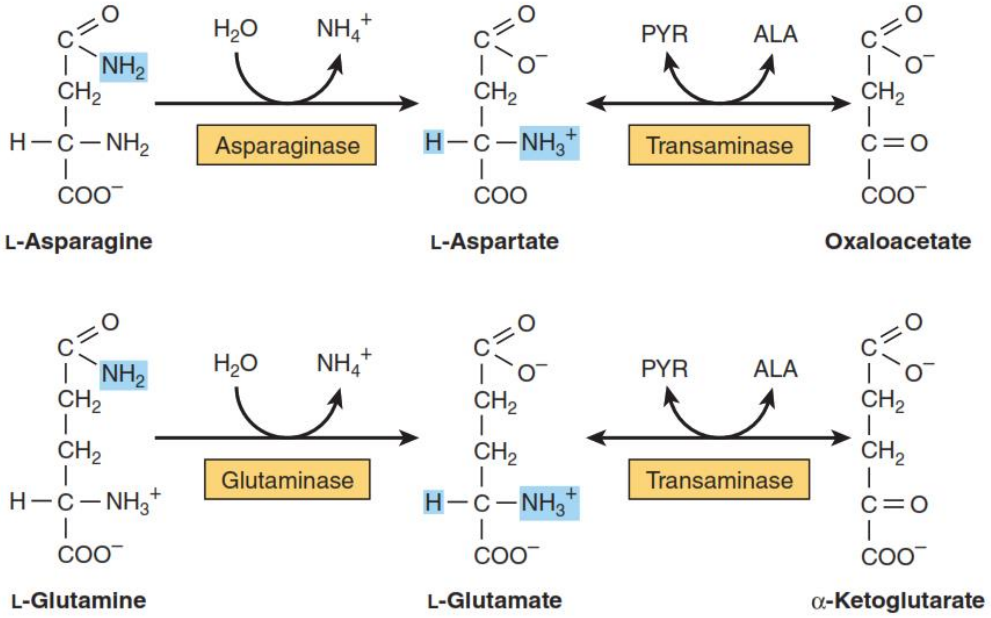
METABOLIC CLASSIFICATION OF AMINO ACIDS

	Glucogenic	Glucogenic and Ketogenic	Ketogenic
Nonessential	Alanine Arginine Asparagine Aspartate Cysteine Glutamate Glutamine Glycine Proline Serine	Tyrosine	
Essential	Histidine Methionine Threonine Valine	Isoleucine Phenyl-alanine Tryptophan	Leucine Lysine

Note



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CONVERSION OF AMINO ACIDS TO SPECIALIZED PRODUCTS

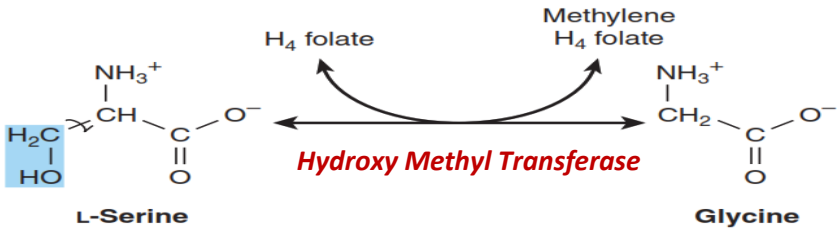
GLYCINE

- **Glycine** is **non-essential** - **glycogenic** amino acid.

SYNTHESIS AND FATES

1- **DENOVO:** **CO2 + NH2 + H2O** $\underset{\text{Glycine cleavage system}}{\overset{\text{Glycine synthase}}{\rightleftharpoons}}$ **GLYCINE**

2- **SERINE:**



3- **THERIONINE:** **THERIONINE** $\xrightarrow{\text{Threonine aldolase}}$ **GLYCINE + Acetaldehyde**

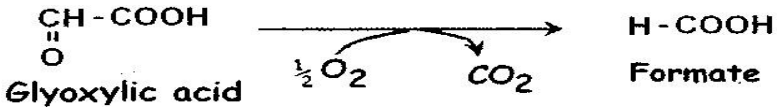
4- **GLYOXILIC ACID:** **BY REAMINATION**

Functions Glycine is the precursor for:

- Heme - Hippuric acid - Glutathione - Glyoxylic acid
- Purine bases - Bile salts - Collagen -Creatine - Serine - Neurotransmitter

1. **Heme:** is the pigment, which combines with globin protein to form hemoglobin.
   - Glycine reacts with Succinyl CoA to form a substance called amino levulonic acid (**ALA**) a reaction needs pyridoxal phosphate. ALA is finally converted to heme.
2. **Hippuric acid:**
   - Glycine conjugates with the toxic compounds like **benzoate** (an additive used to preserve foods) to form the **non-toxic** hippuric acid. This occurs in the **liver**.
3. **Glyoxylic acid**
   - **Synthesis:** Glyoxylic acid is formed from glycine by 2 mechanisms: **oxidative deamination** and **transamination**:
   - **Fate of Glyoxylic acid:**

     a) Formation of formate: (by **oxidative decarboxylation**).



     b) Formation of glycine: By Reamination (**transamination**).

- Primary hyperoxaluria:

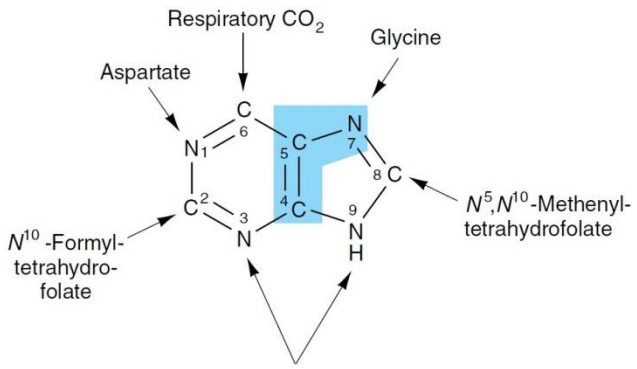
- **Def:** It is a metabolic disease **ccc** by excessive excretion of **Oxalate** unrelated to dietary intake of oxalate. This leads to formation of urinary oxalate stones.
- **Complication:** This condition usually ends by death in early life from either renal failure or hypertension.
- **Causes:** failure of conversion of Glyoxylic a. into formate or glycine. leads to **oxalate** formation.

- **Glycinuria**
- **Def:** It is a rare **dominant x-linked disease ccc** by excess urinary excretion of glycine.
- **Complication:** It leads to formation of **oxalate renal stones**.
- **Causes:** is due to defect in renal tubular reabsorption of glycine.

4. **Glutathione:** It is also called "**γ-glutamyl, cysteinyl glycine**".

- **Structure:** Glutathione is a **Tripeptide** formed of three amino acids: glutamate, cysteine and glycine.
- **Synthesis:** It is synthesized in two Glutathione steps catalyzed by (γ-glutamyl cysteine synthetase and glutathione synthetase).
- **Forms of glutathione:**
  - **Two** Forms are present: **reduced** (G-SH) and **oxidized** (G-S).
  - *-**SH** group indicates the sulfhydryl group of the cysteine and it is the most active part of the molecule.
- **Functions of glutathione:**
  1- **Defense mechanism** against certain toxic compounds (Detoxification).
  2- **Absorption of amino acid:** glutathione has a role in transport of amino acids across intestinal cell membrane..
  3- **Protect against cell damage and hemolysis of RBCs:** Glutathione breakdown the hydrogen peroxide (H_2O_2) which causes cell damage and hemolysis.
  4- **Activation of some enzymes.**
  5- **Inactivation of insulin hormone.**

5. **Bile salts:**
   - These are sodium and potassium salts of glycocholic acid.
   - Glycine is conjugated to cholic acid to form glycocholic acid.
6. **Purine bases:**
   - Carbon atoms NO. **4, 5** and nitrogen atom NO. **7** are derived from glycine.



7. **Collagens:**
   - Collagens are the main proteins of **connective tissue**.
   - All collagen types have a **triple helical structure**.
   - Each helix is formed of **3** amino acids.
   - **Glycine** is present at every third position.

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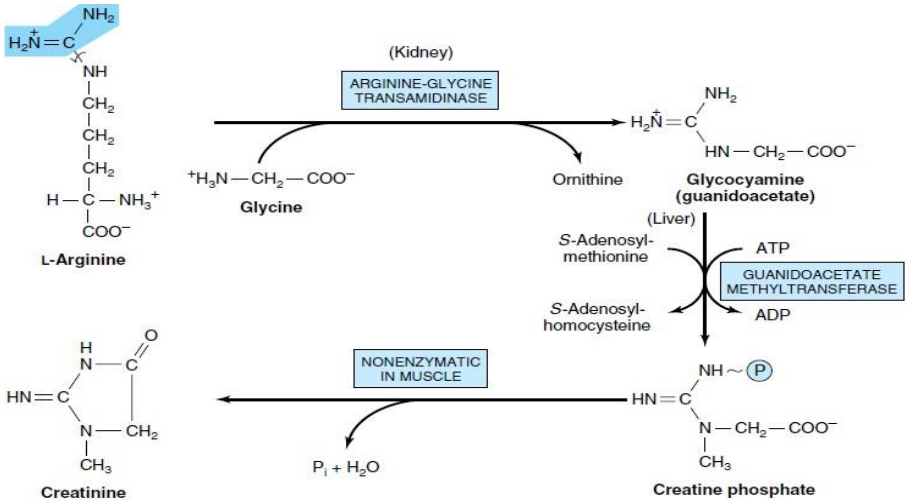
8. **Creatine** (N-methyl-guanidoacetate):

- **Synthesis of Creatine:** It is synthesized from three amino acids: glycine, arginine, and methionine. This occurs by two reactions in **kidney** and **liver**.

a) **In kidney:** the first reaction is **transamdination** i.e. transfer of **guanido** group, H_2N-[C=NH]-NH_2 from Arginine to glycine to form guanidoacetate.

b) **In liver:** the second reaction is **Transmethylation** i.e. transfer of **methyl** group from **S-adenosyl-methionine** to guanidoacetate to form methyl guanidoacetate



- **Functions of Creatine:**
  - Creatine is phosphorylated to Creatine phosphate this occurs in muscles.
  - **Creatine phosphate** acts as a **store** of high energy phosphate in muscles and used during muscle exercise (as it can give phosphate to ADP to form **ATP**).

- **Creatine kinase enzyme (CK):** Also called **Creatine phospho kinase (CPK):**
  - This enzyme catalyses the formation of creatine phosphate. Present in **3** isoenzymes

1) CK-MM: from **skeletal muscles** and its serum level is elevated in muscle disease
2) CK-MB: mainly from **heart muscle** and its serum level is elevated in recent myocardial infarction.
3) CK-BB: derived from **brain** and its serum level is elevated in damage of brain cells.

- **Degradation of Creatine phosphate** → (gives creatinine):

a) Creatine phosphate loses water and phosphate molecules to form a substance called creatinine (= **anhydrous Creatine**).

b) Creatinine is the end product of Creatine metabolism and is normally rapidly removed from the blood and **excreted by the kidney** in urine.

- **Diagnostic importance of determination of plasma creatinine:**

a) Estimation of plasma creatinine (0.6 - 1.2 mg/dl) is used as kidney function test.

b) High blood creatinine (and urea) levels are sensitive indicators of renal failure.

9. **Serine:**

- Methylene H_4 folate is used as **donor** of **one carbon** fragment (-CH_2OH).
- It gives this carbon to glycine to form serine. The reaction is reversible.

10. Neurotransmitter: acts as an inhibitory transmitter in spinal cord and medulla

11. Catabolism of glycine: by enzyme called: glycine **cleavage** system

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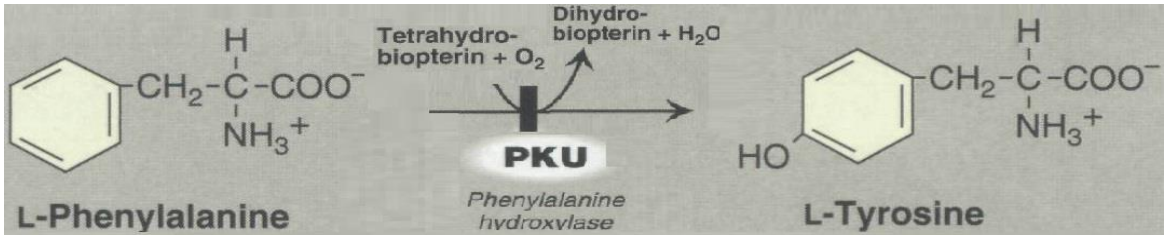
PHENYLALANINE

- **Phenylalanine** is a **Ketogenic and glycogenic essential** amino acid.
- **Functions:** phenylalanine is the precursor for **Tyrosine**. In liver as follows:



- This reaction needs phenylalanine hydroxylase enzyme and tetrahydrobiopterin as coenzyme. This results in the formation of dihydrobiopterin (DHB) which must be regenerated by dihydrobiopterin reductase enzyme with NADPH + H as coenzyme.
- Deficiency of either **phenylalanine hydroxylase** or **dihydrobiopterin reductase** results in a disease called: **PHENYLKETONURIA.**

- **Definition:** It is inherited deficiency of phenylalanine hydroxylase enzyme.
  Atypical phenylketonuria: deficiency of dihydrobiopterin reductase enzyme.
- **Effects (**signs and symptoms):
  1) Mental retardation. (By inhibit of pyruvate translocase enzyme)
  2) Increased blood phenylalanine: due to inability to hydroxylate phenylalanine to tyrosine. & converted it to phenylpyruvate and phenyllactate, which excreted in urine.
  3) Failure to walk and talk. 4) Hyperactivity and tremors.
  5) Failure to grow. 6) An Intelligence Quotient (IQs) 7) Skin lesion e.g. eczema.
- **Frequency of phenylketonuria:** is 1 in 10,000 live births.
- **Diagnosis of phenylketonuria:**
  a) Infants are screened at birth (4th day) by measuring blood phenylalanine by a test called **Guthrie test**, a bacterial assay for phenylalanine.
  - **Prevention of phenylketonuria:**
  a) Any infant proved to have abnormal high level of blood phenylalanine, should feed milk containing **very low** amount of phenylalanine.
  b) This regimen of diet is maintained up to 6 years of age when a high concentration of phenylalanine has no longer effect on brain cells.

TYROSINE

- **Tyrosine** is a **Ketogenic and glycogenic non-essential** amino acid.
- **Tyrosine** becomes essential in case of deficiency of **phenylalanine hydroxylase.**

Functions Tyrosine is the precursor for: **CMT**

1- **C**atecholamines. 2- **M**elanin pigments. 3- **T**hyroid hormones.

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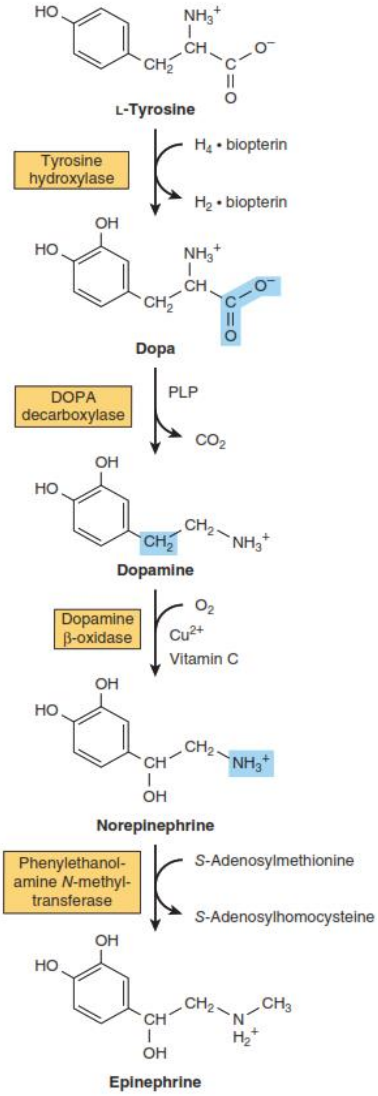
CATECHOLAMINES

These are dopamine, nor-epinephrine and epinephrine.

SYNTHESIS OF CATECHOLAMINES:

They are synthesized from tyrosine at storage sites: **adrenergic neurons** and **adrenal medulla**.

- **In neurons:** nor-epinephrine and dopamine are synthesized from tyrosine as follows:
  1) Tyrosine is first **hydroxylated** to form 3, 4 dihydrophenylalanine (DOPA).
  2) DOPA is then **decarboxylated** to dopamine, which is **hydroxylated** to nor-epinephrine by dopamine hydroxylase.
- **In adrenal medulla:**
  1) Synthesis of catecholamines is similar to synthesis in neurons.
  2) In addition adrenal medullary cells, contain phenylethanolamine N-methyltransferase (PNMT). This enzyme catalyzes the conversion of nor-epinephrine to epinephrine [by **Transmethylation**].

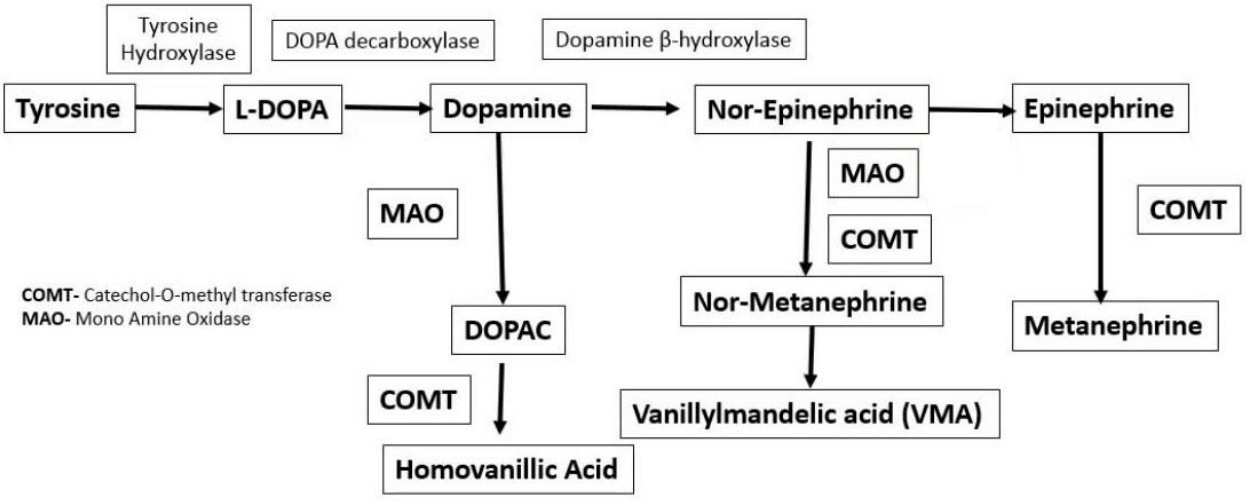


REGULATION OF SYNTHESIS:

Tyrosine hydroxylase is the key enzyme. It is inhibited by feedback inhibition by either **dopamine** or **nor-epinephrine**.

CATABOLISM OF CATECHOLAMINES: by 2 enzymes:

1) Monoamine oxidase (MAO): present mainly in the mitochondria of adrenergic nerve
2) Catechol-ortho-methyl transferase (COMT): which is present in all tissues, with high concentration in the liver and kidney, but not found in the nerve endings.



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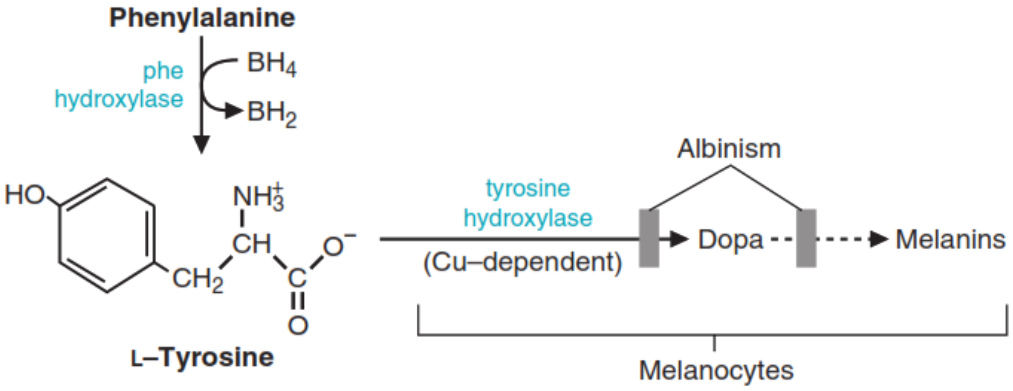
2-MELANIN PIGMENTS

SYNTHESIS OF MELANIN

In the skin, melanins are synthesized in melanocytes (pigment forming cells) by **tyrosine hydroxylase** (tyrosinase) enzyme.



FUNCTIONS OF MELANIN

a) Melanins are pigments present in many tissues particularly in the iris, hair and skin.

b) Melanins are synthesized to protect underlying cells from the harmful effects of sunlight.

3. THYROID HORMONES

SYNTHESIS OF THYROID HORMONES

a) Synthesis and release of T3 and are stimulated by (TSH).

b) TSH secretion is under control of thyrotropin releasing hormone (TRH) which is a Tripeptide hormone produced in the hypothalamus.

- By feedback mechanism: Increased levels of plasma T_3 and T_4 inhibit the secretion of TRH from hypothalamus and TSH from pituitary gland.

STEPS OF THYROID HORMONES SYNTHESIS

1) The thyroid gland contains many follicles, each composed of a shell of single layered cells surrounding a central space filled with glycoprotein called: thyroglobulin (TG).

2) Thyroglobulin contains about 150 tyrosine residues.**3)** Iodide ions (I^-) can be taken up by thyroid cells and oxidized into higher value state (positive ions, I^+). This needs H_2O_2 and thyroid peroxidase enzyme.

4) I^+ is then incorporated into the tyrosine residues of TG.

5) The resulting Monoiodotyrosine and Diiodotyrosine residues react together to give one of the following compounds:

a. Tetraiodotyrosine {thyroxin, T4}. b. Triiodotyrosine {T3}. c. Reverse {rT}.

6) Both T_3 and T_4 are biologically active, while rT_3 is biologically **in**active.

7) Enzyme hydrolysis of thyroglobulin releases free T_3 and T_4 into the plasma.

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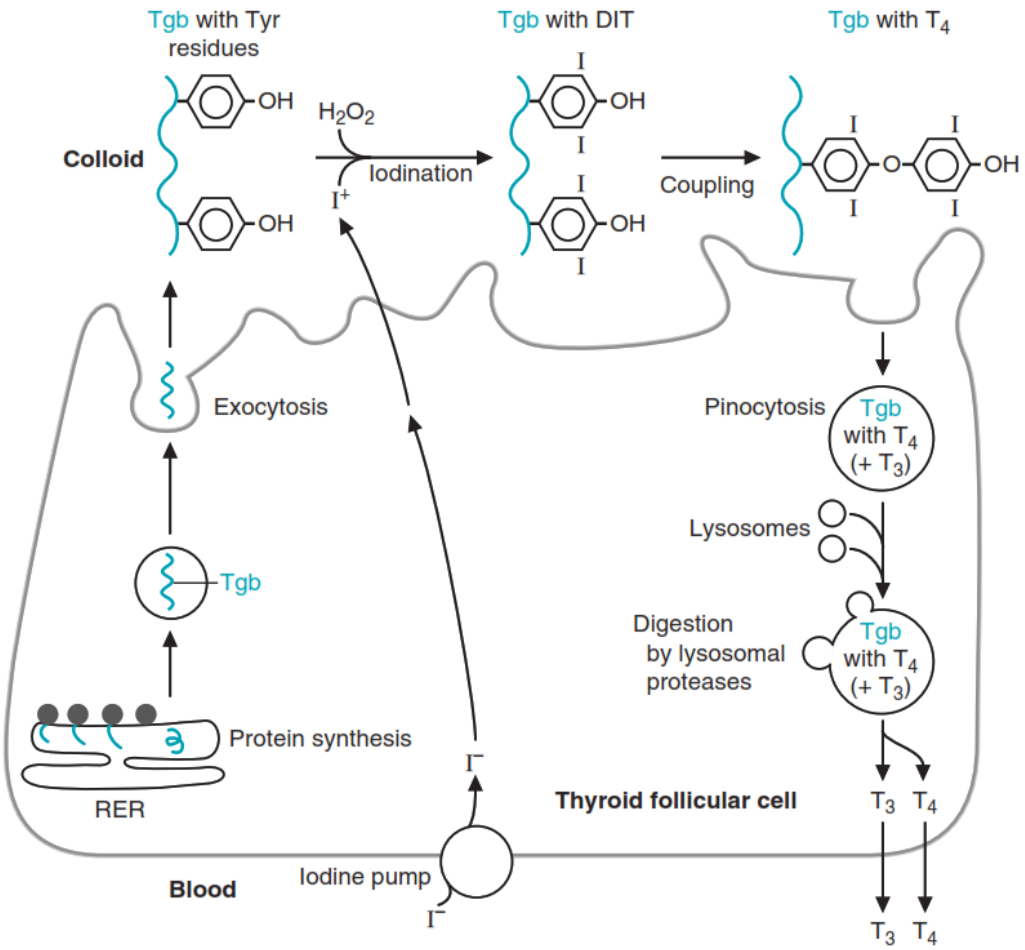

FUNCTIONS OF THYROID HORMONES:

a) They increase heat production and oxygen consumption in most tissues through stimulation of ATPase activity.

b) They regulate the growth of long bones (together with growth hormone).

c) They affect protein synthesis through stimulation of DNA in the nucleus of cells.

d) They increase catecholamine effect.

- **Plasma T_3 and T_4:**

a) In the plasma 99.95% of T_3 and T_4 are transported in association with 2 proteins:

1) Thyroxin binding globulin (TBG). **2) Thyroxin binding prealbumin**.

b) About 0.05 % of T_3 and T_4 are Free T3 and T4 "active" hormones in the plasma

Hypothyroidism

- Def: ↓ amounts of free T_3 or T_4.

- Cause: thyroid failure

can be due to disease of the pituitary or hypothalamus.

- The thyroid hormones insufficiency during intrauterine fetal life results in a disease shows **abnormal physical** development and **mental retardation** (cretinism).

Measurement of T3, T4 and TSH must be done for every newly born infant

- If the disease occurs later in life, it is called: (myxodema),

Hyperthyroidism

(thyrotoxicosis)

- Def: ↑production of T_3 or T_4

- Cause: Most cases are due to Graves disease which results from the production of antibodies that activate TSH production and in turn produces excessive amounts of T_3 and T_4.

These antibodies are called: Thyroid-stimulating IgG (TSI).

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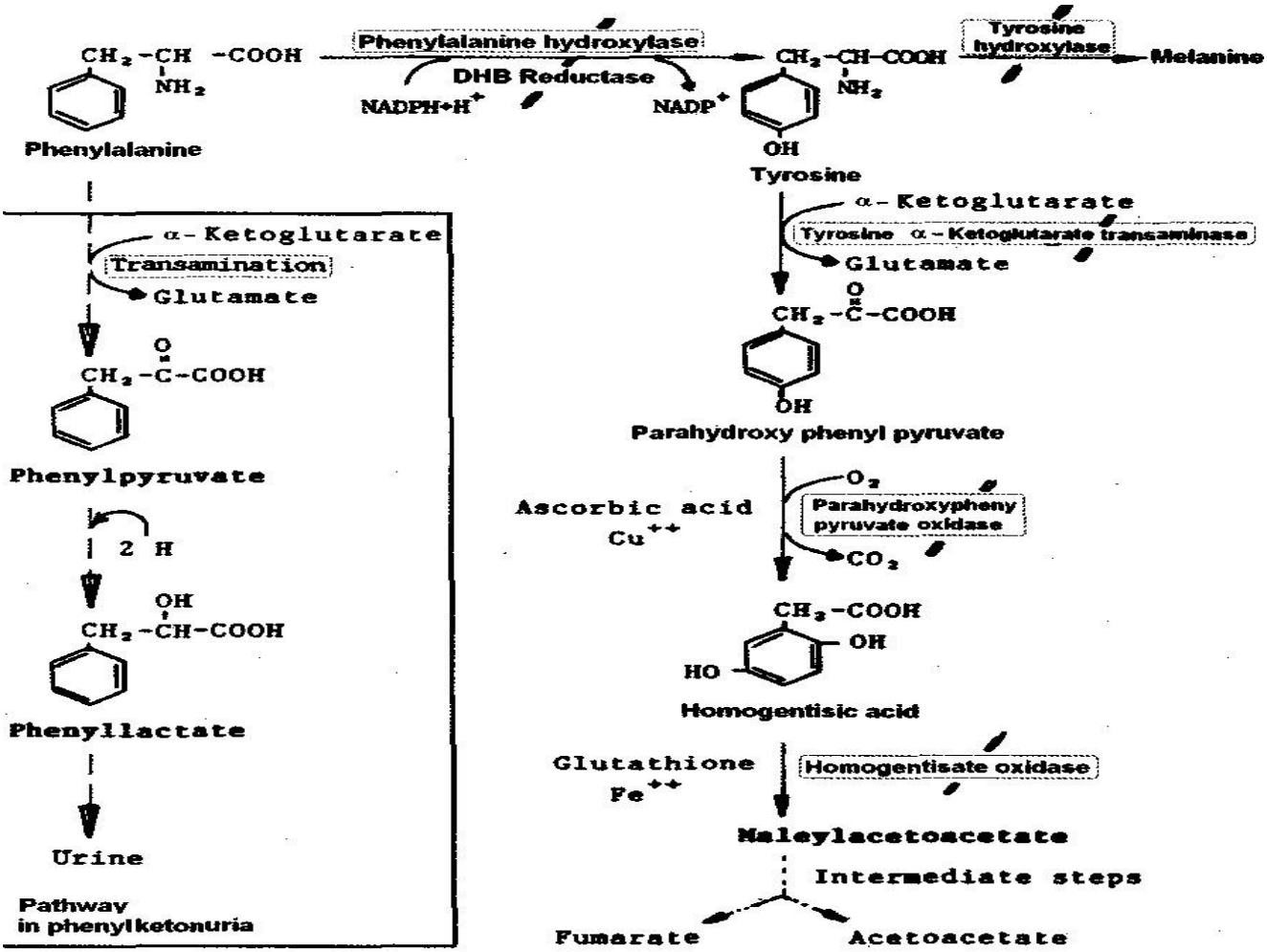
CATABOLISM OF PHENYLALANINE AND TYROSINE

The carbon skeletons that have left after the removal of amino groups of both phenylalanine and tyrosine may catabolize to form Fumarate (glycogenic) or acetoacetate (Ketogenic).



INBORN ERRORS OF TYROSINE METABOLISM

1- Hereditary tyrosinemia (tyrosinosis):

- **Def:** It is inability to metabolise **tyrosine** and **p-hydroxy phenylpyruvate**.
- **Cause:** deficiency of tyrosine **α-Ketoglutarate transaminase** and **p-hydroxy-phenylpyruvate oxidase** enzymes
- **Forms of tyrosinemia:**

a) **Acute:** where there is diarrhea, vomiting and failure to grow. Death from liver failure occurs within **7** months.

b) **Chronic:** occurs later in life. **Liver cirrhosis** and **hepatic carcinoma** are common. There is also a mild mental retardation. **For unknown cause methionine level may be high**.

- **Prevention and treatment:**
- Feeding the affected infant and children a diet containing very low levels of tyrosine and phenylalanine (precursor of tyrosine).

2. Alkaptonuria:

- **Def:** benign disease resulting from deficiency of homogentisate oxidase enzyme.
- **Effects:** Homogentisate increases and causes:

a) Deposition in joints causing **arthritis**.

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b) Deposition in connective tissue causing generalized pigmentation (**ochronosis**).

c) Excreted in large amounts in urine, that is oxidized in the air giving the **dark urine**

3. Albinism:

- **Def:** hereditary deficiency of tyrosine hydroxylase enzyme in melanocytes. - **Effects:** defective synthesis of melanin pigments. Eye, skin and hair are affected.
- **Types of albinism:** according to the site affected:

a) Eye: ocular albinism. **b) Skin:** cutaneous albinism.

c) Eye and skin: oculo-cutaneous albinism.

Tryptophan

- It is **glycogenic and ketogenic essential** amino acid.
- **Functions:** Tryptophan is the precursor of: **SMNI**

1. Serotonin. **2. M**elatonin. **3. N**iacin (nicotinic acid) **4.I**ndole and skatole.

SEROTONIN

Also called 5-hydroxytryptamine.

SYNTHESIS OF SEROTONIN

- Tryptophan is hydroxylated in a reaction similar to that of phenylalanine. The product **5-hydroxytryptophan** is decarboxylated to **serotonin**.

- **Storage sites of secretion & Functions of serotonin::**

a) Hypothalamus and brain stem → Neurotransmitter: it is stimulatory one.

b) Pineal gland (body) → regulate circadian rhythm.

C) Argentaffin cells in intestinal mucosa→ Contraction of smooth muscle fibers.

d) Platelets → Vasoconstriction.

CATABOLISM OF SEROTONIN

- Serotonin undergoes oxidative deamination by monoamine oxidase (MAO). The resulting compound, 5-hydroxyindol acetic acid is excreted in urine.
- Certain substances can inhibit MAO enzyme e.g. iproniazide drugs. This causes increase of serotonin, a stimulatory transmitter in brain. These drugs are used in treatment of psychic conditions as **depression.**

Argentaffinoma (carcinoid syndrome):

- **Def:** **malignant disease characterized by excessive production of serotonin**
- **Complication:** **↓niacin synthesis → signs of pellagra developed, diarrhea and broncho-spasm**
- **Diagnosis:** **Urinary excretion of 5-hydroxyindol acetic acid is increased.**

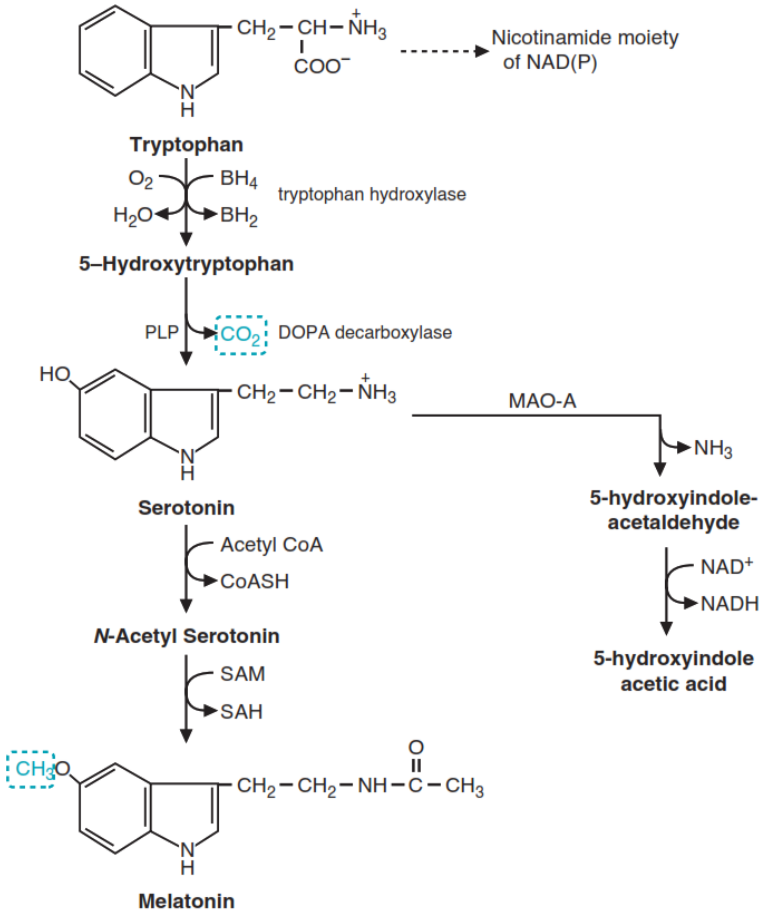
Melatonin

SITE OF SECRETION: pineal gland

SYNTHESIS OF MELATONIN:

a) It is synthesized in pineal gland, as the **acetyl transferase** needed for melatonin synthesis is present in pined gland. Melatonin is synthesized from serotonin by acetylation followed by methylation.

b) Melatonin is secreted only at night (dark). This is because the release of melatonin **is inhibited by light entering the eye and transmitted to the pineal gland by way of the CNS.**



FUNCTIONS OF MELATONIN

a) It inhibits gonadal functions.

b) It has sleep inducing effect.

c) It inhibits synthesis and secretion of other neurotransmitters: dopamine and GABA.

d) Regulation of circadian rhythm, being synthesized mostly at night.

NIACIN (NICOTINIC ACID)

SYNTHESIS OF NIACIN

a) It is synthesized in the course of tryptophan catabolism.

b) Every **60** mg tryptophan are converted into **1** mg niacin.

FUNCTIONS OF NIACIN

Niacin is a member of **vitamin B complex**, being synthesized in liver.

a) It is essential for synthesis of **NAD** and **NADP** coenzymes, which act as hydrogen carriers in varieties of metabolic reactions.

b) Niacin lowers plasma cholesterol. This is because it inhibits the flow of free fatty acids (FFA) from adipose tissue, which provides acetyl CoA essential for cholesterol synthesis.

PELLAGRA

a) This is a disease resulting from deficiency of niacin formation.

b) It results from deficiency of either niacin tryptophan, or pyridoxine.

c) It is the disease of 4Ds. These are diarrhea, dermatitis, dementia and death.

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INDOLE AND SKATOLE

1. These are putrefactive products of tryptophan produced by bacteria in large intestine.
2. Indole and skatole give the characteristic odor of stool.
3. Indole and skatole may be absorbed and go to the liver to be hydroxylated and conjugated with sulphate and excreted in urine as salt forms:

- Potassium skatolxyl
- Sulphate and potassium indoxyl sulphate (=**indican**).

HARTNUP'S DISEASE:

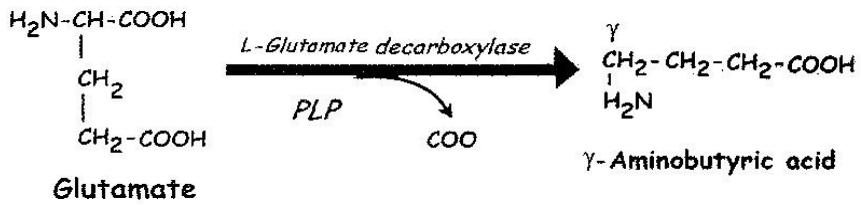
- **Def:** hereditary abnormality in tryptophan metabolism where the intestinal absorption and renal tubular reabsorption of this amino acid are impaired.
- **Characters:** by pellagra skin rashes, psychiatric changes and mental retardation.
- There is excess excretion of tryptophan together with lysine and histidine in urine (aminoaciduria).
- **ttt:** Administration of Nicotinamide usually relieves all symptoms except aminoaciduria.

GLUTAMIC ACID

- **Glutamic acid** in **nonessential glycogenic** amino acid.
- **Functions of glutamic acid:** **Remove GEFN**

1. Removal of amino group of most amino acids.
2. Glutathione synthesis
3. Glutamine synthesis
4. Gamma amino butyric acid (GABA).
5. Enzyme activator.
6. Folic acid synthesis.
7. Neurotransmitter.

- **Removal of amino group of most amino acids:** in the form of **ammonia** through Transdeamination.
- **Glutathione synthesis:** (See glycine metabolism).
- **Glutamine synthesis:** (See fate of ammonia).
- **Enzyme activator:**
  N-Acetyl glutamate activates Carbamoyl phosphate synthase **I** enzyme (see urea biosynthesis).
- **Folic acid synthesis:**
  - Folic acid is a member of vitamin B-complex being composed of pteridine base, Para-amino benzoic acid (PABA), and one or more glutamic acid residues.
  - **Function:** acts as a carrier of one carbon units, which has important role in amino acid metabolism and Purine and pyrimidines synthesis.
- **Neurotransmitter:**
  Glutamate acts as excitatory neurotransmitter in all CNS neurons.
- **Gamma amino butyric acid (GABA):**
  - **Synthesis of GABA:**
    - It is synthesized from L-glutamate by L-glutamate decarboxylase in the presence of pyridoxal phosphate as coenzyme.



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- **Functions of GABA:**

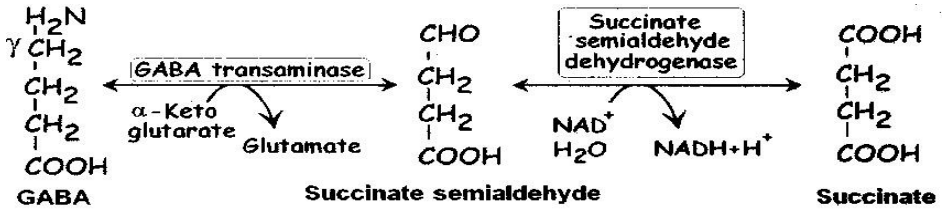
  - It is an inhibitory transmitter in brain and spinal cord.

  a) In the brain, GABA is a postsynaptic inhibitory transmitter.

  b) In the spinal cord, GABA is pre-synaptic inhibitory transmitter.

- **Catabolism of GABA:**

  - It is metabolized within the neurons to Succinate:



- **Deficiency of GABA:**

  a) It may be due to deficiency of either: L-glutamate decarboxylase or pyridoxal phosphate.

  b) It causes convulsions especially in children.

ASPARTATE

- It is **non-essential glycogenic** amino acid.

- **Functions of Aspartate: papun β**

- **P**urine formation
- **A**sparagine
- **P**yrimidines formation
- **U**rea formation
- **N**eurotransmitter
- β-Alanine

➢ **Purine formation:**

Aspartate is the source of N_1 of Purine.

➢ **Pyrimidines formation:**

Aspartate is the source of N_1, C_4, C_5 and C_6 of pyrimidines.

➢ **Urea formation:**

Aspartate reacts with citrulline to form arginosuccinate.

➢ **Asparagine formation:**

- **Functions:**

a) It enters in the structure of some proteins e.g. **oxytocin** hormone.

b) It is a source of ammonia especially in plants.

➢ **Neurotransmitter:**

Aspartate acts as an excitatory transmitter on all CNS neurons.

➢ **β-Alanine:**

- In bacteria, decarboxylation of aspartic acid produces β-Alanine.
- In mammalian tissues β-alanine arises during catabolism of cytosine base.
- β-Alanine enters in the structure of: pantothenic acid, coenzyme A, carnosine, anserine and homocarnosine.

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ARGININE

- It is **glycogenic, semi-essential amino** acid i.e. formed in amount not sufficient for body especially in children and pregnant females.

- **Functions of Arginine: CANU**

- **Creatine formation:** see glycine metabolism.
- **Arginine phosphate (Arginine — P)**: it is present in muscles and acts as a source of energy in animals (invertebrate).
- **Urea formation:** see urea cycle.
- **Nitric oxide:** L-Arginine serves as a precursor of nitric oxide (NO).

1. **NO** is an **intracellular** signaling molecule and functions as neurotransmitter, smooth muscle relaxant and vasodilator (through **cGMP**).

- **NO synthase** is a complex enzyme using 5 cofactors: *NAD*, *FAD*, *FMN*, *heme* and *tetrahydrobiopterin*

2. Nitroglycerine (glyceryl trinitrate) is a powerful coronary vasodilator through increasing **NO** formation.
3. Sildenafil (Viagra) is a drug that **inhibits phosphodiesterase** enzyme that converts **cGMP** into **GMP**. This maintains the action of **cGMP** as smooth muscle relaxant and vasodilator and used as a drug that maintains penile erection.

ORNITHINE

- It is a **glycogenic, non-essential** amino acid.

- **Functions:** Ornithine is important for:

➢ **Urea formation.**

➢ **Detoxication:**

Ornithine + Phenyl acetyl CoA (Toxic) → Phenyl acetyl ornithine (non-toxic).

➢ **Spermidine and spermine formation:** These are polyamines formed in prostate by ornithine and methionine.

- **Functions:**

a) Cell proliferation (division) and growth.
b) Stabilization of intact cells, cell membrane and sub-cellular organelles.
c) They give the characteristic odor of **semen**.
d) Stimulation of **DNA** and **RNA** biosynthesis.
e) Inhibition of protein kinase enzyme.
f) In pharmacological doses, polyamines cause decrease in both blood pressure (hypotension) and body temperature (hypothermia).

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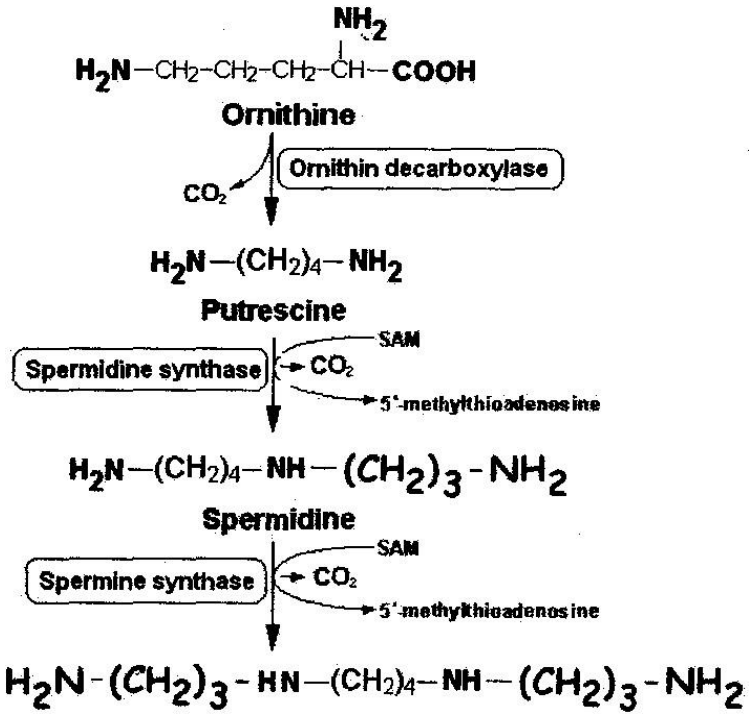
- **Biosynthesis:**



- **Catabolism:**

  a) Spermine is oxidized to **Spermidine** and **putrescine**.

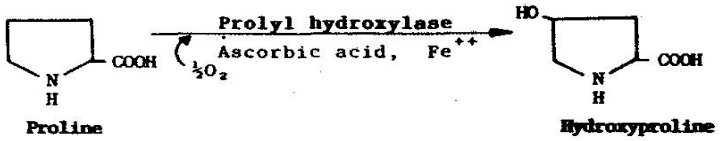
  b) Both are either excreted in urine or converted to **CO_2** and **NH_3**.

PROLINE ANT HYDROXYPROLINE

- These are **non-essential glycogenic** imino acids.

- Functions of proline:

➢ **Hydroxyproline synthesis:**



➢ **Collagen synthesis:**

1. Proline and hydroxyproline are very rich in collagen.
2. Ascorbic acid deficiency leads to a weak collagen (scurvy).

- **Catabolism of proline:** gives glutamate.

CYSTEINE

- Cysteine is glycogenic, non-essential amino acid.

- Functions: It enters in the synthesis of:

- **G**lutathione
- **T**aurine
- **T**hioethylamine
- **P**roteins
- **D**etoxication

➢ **Taurine:**

- **Synthesis:**

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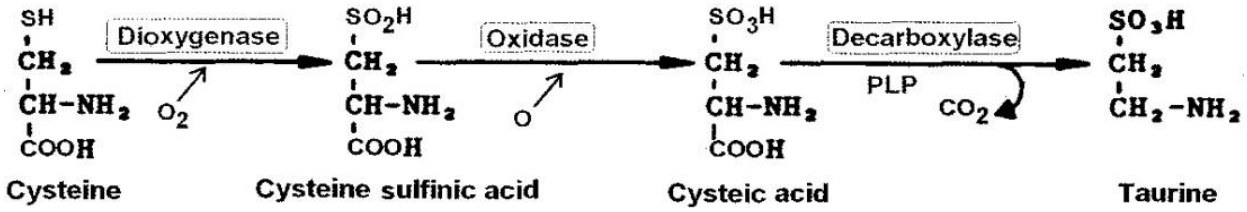


- **Functions:**

It combines with cholic acid to form taurocholic acid. Its sodium salt (sodium taurocholate) is one of bile salts, which are Important for digestion, and absorption of lipids.

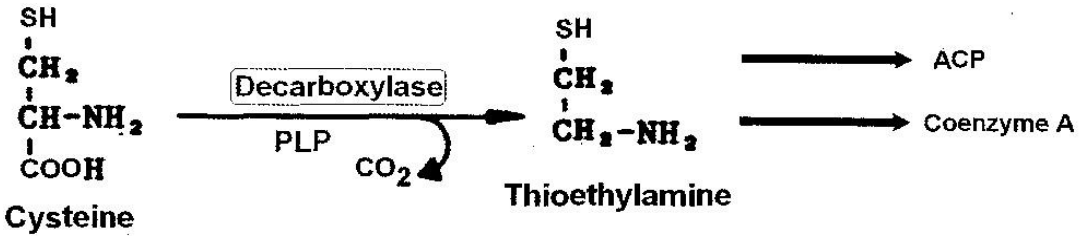
➢ **Thioethylamine:** A part of the vitamin: Pantothenic acid.

- **Functions: it enters in the structure of:**

a) Coenzyme A: It is a coenzyme, which is important in carbohydrates and lipids metabolism.

b) Acyl carrier protein (ACP): This is a component of fatty acid synthase enzyme.

- **Synthesis:**



➢ **Protein synthesis:** Cysteine is very important amino acid for some proteins as:

1. Keratins: simple proteins that are present in hair, nail, skin etc. Keratins are very rich in cysteine.

2. Many enzymes: e.g. **glyceraldhyde-3-phosphate dehydrogenase** contains in its active center **-SH** group derived from cysteine.

➢ **Detoxication:** Cysteine is important for the detoxication of some aromatic compounds e.g. bromobenzene.

CYSTINE

- **Cystine** (di-cysteine) is glycogenic, non-essential amino acid.
- **Functions:**

➢ **A. Protein structure:** The -S-S- group of cystine is important for tertiary and quaternary structure of proteins e.g. insulin hormone has two -S-S- groups.

Cystinuria (cystine - lysinuria):

- **Def:** hereditary disease characterized by amino aciduria (excessive excretion of cystine together with basic amino acids; lysine, Arginine, and ornithine.
- **Cause:** defective renal tubular reabsorption of these 4 amino acids. Cystine may precipitated in renal tubules forming renal stones.

HOMOCYSTEINE

- Homocysteine test measures the amount of the amino acid in the blood.
- Homocysteine may get high levels when cholesterol, white blood cells, calcium, and other substances (plaque) build up in blood vessels. This build-up may lead to a heart attack. Stroke. And blood clots in the lungs (pulmonary embolism) or deep veins of the legs (deep venous thrombosis).

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METHIONINE

i. Methionine is glycogenic, essential amino acid.

ii. Function: It enters in the synthesis of:

A. Cysteine synthesis: Through formation of Homocysteine, this reacts with **serine** to give **cysteine**.

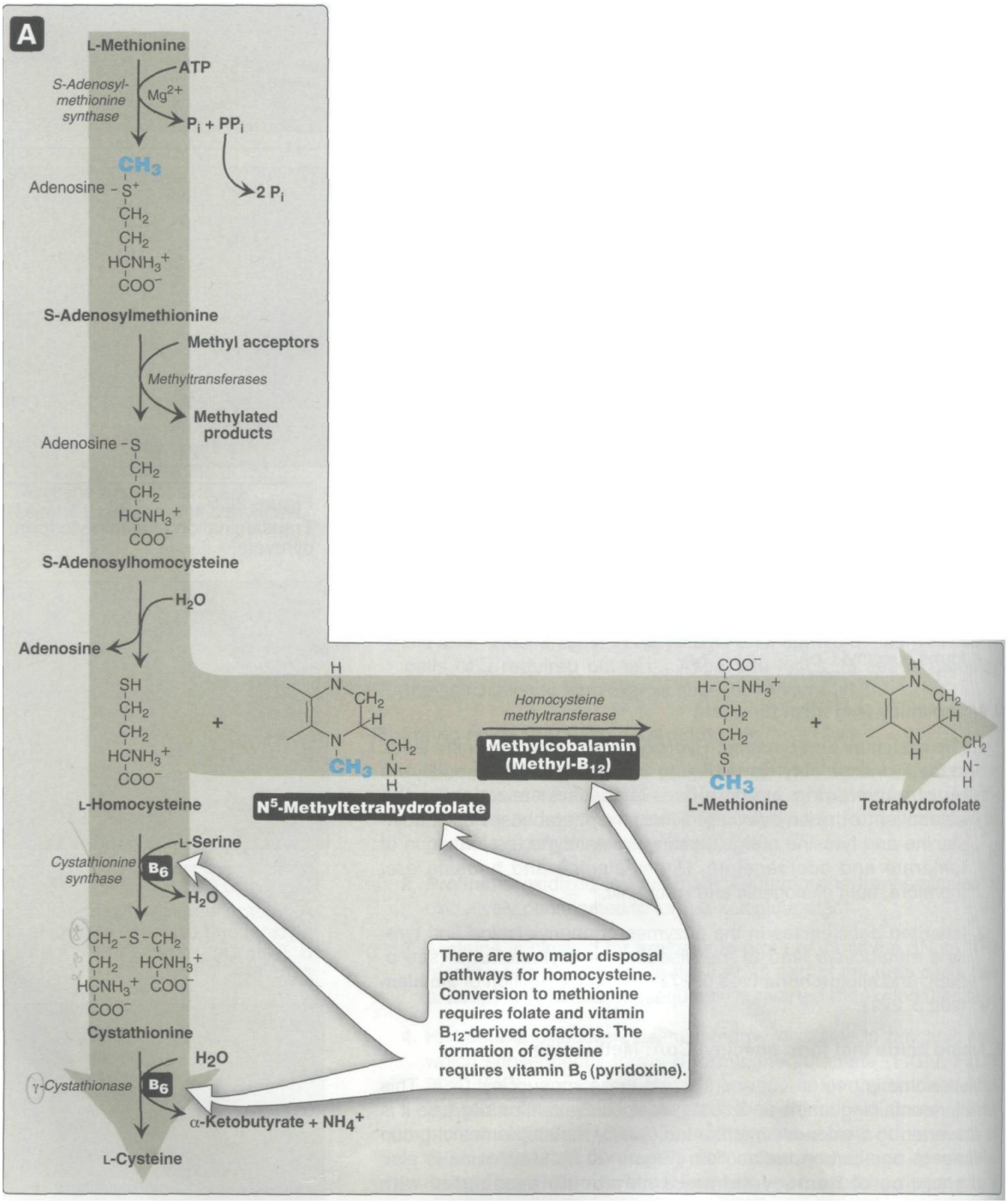
B. Lipotropic factor: Methionine is one of lipotropic factors, which prevent **fatty liver**.

C. Spermidine and spermine: see ornithine metabolism.

D. S-Adenosyl methionine (SAM): The main **methyl donor**, used in Transmethylation reactions.

Transmethylation reactions.

- **Def:** the transfer of **active methyl group** from a **methyl donor** to a **methyl acceptor**.
- **Formation:** SAM is a high energy compound resulting from a condensation of **methionine** with **ATP** with hydrolysis of **all** phosphate bonds in **ATP**.



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- **Catabolism:** - After giving the **methyl group** to a methyl acceptor, **SAM** is converted to S-adenosyl Homocysteine, which is then hydrolyzed to **Homocysteine** & **adenosine**.

- **Homocysteine has two fates:**

1) Synthesis of cysteine:

i- Homocysteine can combine with serine forming cystathionine by **cystathionine synthtase**

ii- Cystathionine is hydrolyzed to L-Homoserine and cysteine by **cystathionase**.

iii- Homoserine → α-Keto butyrate → oxidatively decarboxylated to form → Propionyl COA → Succinyl CoA → glucose.

2) Re-Synthesis of methionine:

i- Homocysteine can accept a methyl group from **methyl tetrahydro-folate** (Me-H4-Folate) in a reaction requiring cobalamine (B12) as an intermediate cofactor.

- **Examples:**

	SAM		SAH
1. Nor-epinephrine	→	methyl-transferase	epinephrine.
2. N-acetyl serotonin	→		melatonin.
3. Ethanolamine	→		Choline.
4. Guanido acetate	→		Creatine.
5. Pyridine	→		N methyl pyridine.

HOMOCYSTANURIA:

* This is a hereditary disease due to deficiency of **cystathionine β-synthase**
* Plasma methionine levels are elevated.
* There is excessi ve urinary excretion of **Homocysteine** and **SAM**
*sig and symptoms include: mental retardation, thromboses, osteoporosis and dislocation of eye lenses.
***Treatment:** feeding a diet low in methionine high in cysteine.

HISTIDINE

I. It is essential, glycogenic amino acid.

It is used for synthesis of: **A. HISTAMINES**

1. Functions: Histamine is secreted by **mast cells** as a result of allergic reactions or trauma. It has the following functions: a) Vasodilatation. b) Contraction of smooth muscles of bronchi. c) Stimulation of gastric secretions.

2. Synthesis:

Histamine is derived from histidine by **decarboxylation**. This reaction is catalyzed by either 2 different enzymes: **a)** Aromatic L-amino acid decarboxylase or **b)** Histidine decarboxylase.

B. Ergothionine:

1. It is N-trimethyl, thiol histidine. 2. Ergothionine is an intracellular antioxidant naturally occurring in plants and animals.

C. Carnosine and Anserine:

1. Carnosine is a substance results from conjugation of **histidine** with **β-alanine**.
2. **Anserine** is produced by **methylation** of **carnosine**.
3. Both are present in skeletal muscles and not in cardiac muscle.

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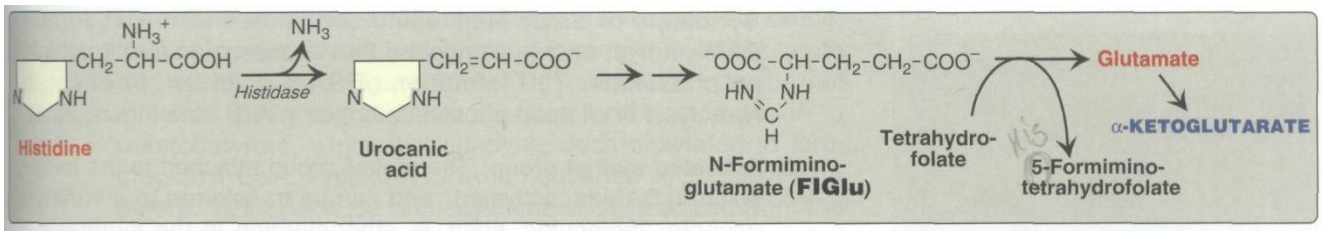
4. Functions:

a) Anserine and carnosine activate myosin ATPase enzyme.

b) They have antioxidant activity and have a role in copper metabolism.

- **Catabolism of Hisidine:** is deaminated to **urocanic** acid, which is converted to **4-imidazolone 5-propionate**. Hydrolysis of the later, **gives N-formiminoglutamate (FIGlU)** , which donates its formimino group to **tetrahydro-folate** , leaving glutamate which is then converted to a-Ketoglutarate.

a) FIGLU excretion test: Deficiency of folic acid + excretes increased amount of FIGIU in urine. It is useful test of **folic** acid deficiency.



HISTIDINEMIA:

* This is a hereditary disease due to deficiency of **histidase** enzyme.

* It is characterized by mental retardation and speech defects.

SERINE

I. Serine is non-essential, glycogenic amino acid.

II. Serine is used for the synthesis of:

A. Phosphoprotein: The -OH group of serine residues present in proteins is the site of etherification of phosphate to form phosphoprotein.

B. Sphingosine base: Serine reacts with palmityl CoA to form sphingosine base. It enters in the structure of **Sphingomyelin**

C. Cysteine: Serine reacts with Homocysteine (derived from Adenosyl methionine) to form cysteine.

D. Purine bases: n-carbon of serine enters in the formation of C_2 and C_5 of Purine

E. Glycine: Through the action of serine hydroxy methyl transferase.

F. Ethanolamine and choline: Serine, ethanolamine and choline are important constituents of phospholipids.

Alanine and β-alanine

I. These are non-essential, glycogenic amino acid

ii. Alanine is important for:

A. Alanine -together with glycine- forms a major fraction of **plasma amino acids**.

B: Alanine is the main amino acid that is converted into glucose in liver through **alanine-glucose cycle**.

G. Alanine is a major component of bacterial cell wall.

- β-Alanine is important for the synthesis of:

A. Pantothenic acid, anserine acid carnosine.

B. -Alanine does not enter in the formation of proteins.

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Threonine

I. It is essential, glycogenic amino acid.

II. Threonine is used for the synthesis of:

A. Phosphoproteins: Like serine, the -OH group of threonine is important for. the **synthesis of** Phospho-proteins.

B. Glycine: Through the action of threonine aldolase enzyme.

LYSINE AND HYDROXYLYSINE

I. Lysine is an essential, ketogenic & glucogenic amino acid.

II. Lysine is important for Hydroxylysine synthesis:

A. Collagen synthesis: Lysine and hydroxylysine are very rich in collagen.

B. Carnitine synthesis: 1. It is 3-hydroxy, y-trimethyl amino butyric acid.

2. It is synthesized from lysine, at first by **methylation** (using S-**adenosyl methionine**), then **deamination** and finally by **removal of 2** carbons to give Carnitine.

3. Functions: Carnitine acts as a carrier, transporting long chain acyl CoA across inner mitochondrial membrane. This is essential for fatty acid oxidation

BRANCHED CHAIN AMINO ACIDS

Valine - Leucine – Iso-Leucine

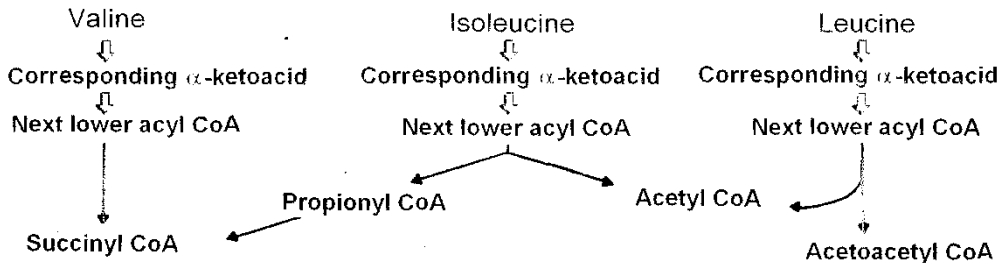
1. All are essential amino acids.
2. Valine is glycogenic, Leucine is Ketogenic and Isoleucine is glycogenic and Ketogenic.
3. All enter in the formation of body proteins.

- Catabolism:

- The **transamination** of the branched chain amino acids occurs mainly in muscle, brain and adipose tissue. Liver is deficient in transaminase required for their transamination.
- The **α-ketoacid,** which result from the transamination reactions are **oxidatively decarboxylated** by α- **ketoacid decarboxylase** to give **acyl CoA** that is less than a-keto acid by one carbon atom. This reaction is similar to that catalyzed by pyruvate dehydrogenase complex.
- The acyl CoA will be oxidized through several steps to give:

a) Succinyl CoA: this is for valine (glycogenic).

b) Acetyl CoA, acetoacetyl CoA: this is for Leucine (Ketogenic).



Summary of catabolism of branched chain amino acids

MAPLE SYRUP URINE DISEASE:

a) Definition: It is accumulation of α-ketoacid of branched chain amino acids and their excretion in urine.

b) Cause: it results from deficiency of oxidative decarboxylation of α-ketoacid.

c) Effects: 1. Mental retardation. 2. Urine has a maple syrup odor or burnt sugar.

3. Children do not usually live more than 1 year.

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PROTEIN DISEASE

	DISEASE	DEFICIENCY OF	EFFECT
GLYCINE	GLYCINURIA	- ↓renal reabsorption of glycine - dominant x-linked disease	- oxalate renal stones
	PRIMARY HYPEROXALURIA	failure of conversion of Glyoxylic acid into formate or glycine	- renal failure or - Hypertension. - death in early life
METHIONINE	HOMOCYSTANURIA	cystathionine β-synthase	- mental retardation, - thromboses, - osteoporosis and
PHENYLALANINE	PHENYLKETONURIA	- phenylalanine hydroxylase or - dihydrobiopterin reductase	- Mental retardation - Failure to walk and talk. - Hyperactivity and tremors - An Intelligence Quotient (IQs) -Skin lesion e.g. eczema
TYROSINE	TYROSINOSIS	- tyrosine α-Ketoglutarate transaminase and - p-hydroxy-phenylpyruvate oxidase	- Liver cirrhosis and - hepatic carcinoma - mental retardation
	ALKAPTONURIA	Homogentisate oxidase	- arthritis - ochronosis - dark urine
	ALBINISM	- tyrosine hydroxylase	Defective synthesis of melanin pigments. Eye, skin and hair are affected
TRYPTOPHAN	HARTNUP'S DISEASE	- intestinal absorption - renal tubular reabsorption	- pellagra skin rashes, - psychiatric changes and mental retardation
BRANCHED CHAIN AMINO ACIDS	MAPLE SYRUP URINE DISEASE	oxidative decarboxylation of α-ketoacid	- Mental retardation. - Urine has a maple syrup odor or burnt sugar
CYSTINE	CYSTINUREA	↓ renal reabsorption of cystine	- Crystaluria - stone formation
	CYSTINOSIS	Defect of transport system of tyrosine.	

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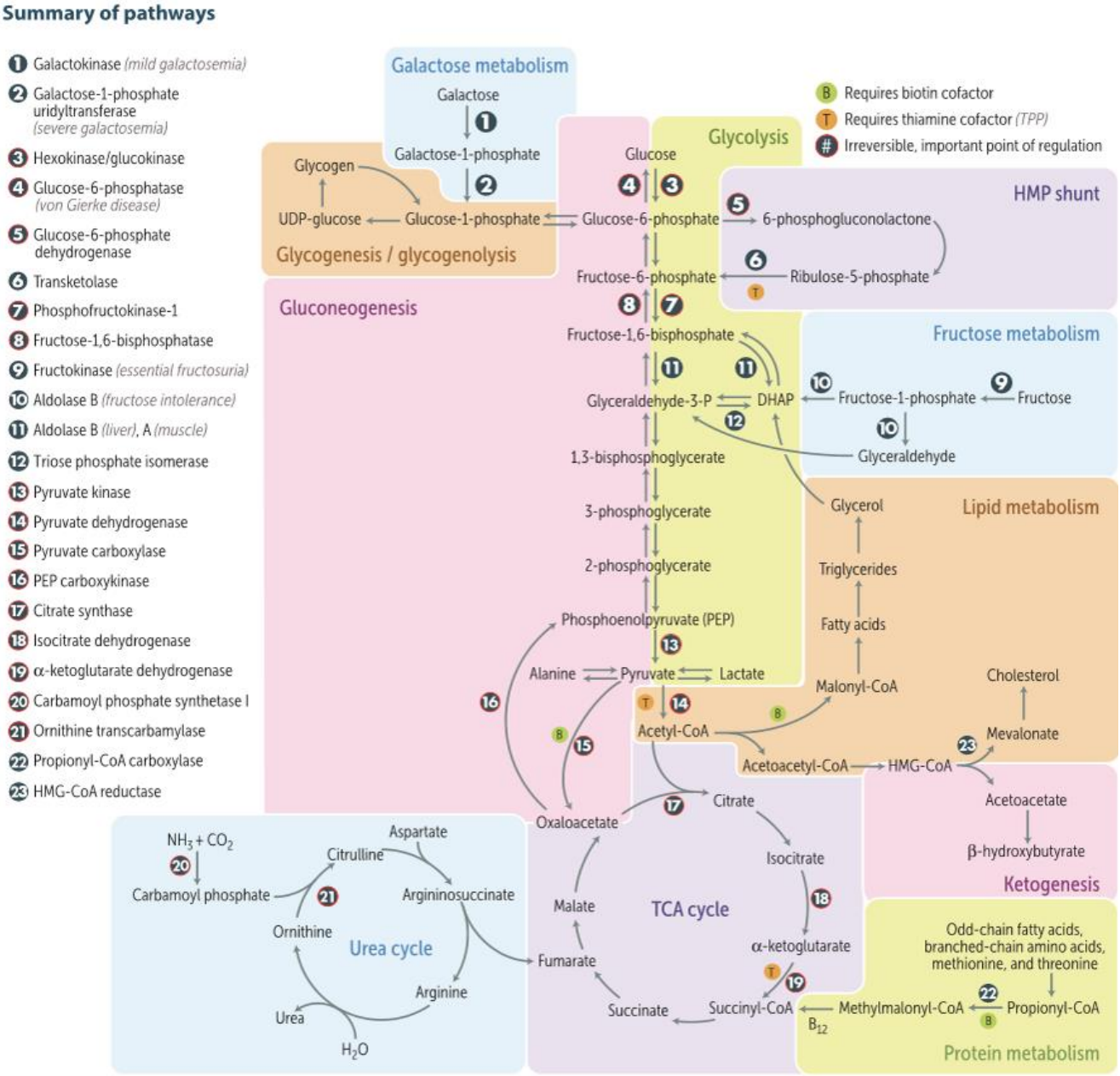

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CHAPTER 8

Vitamins

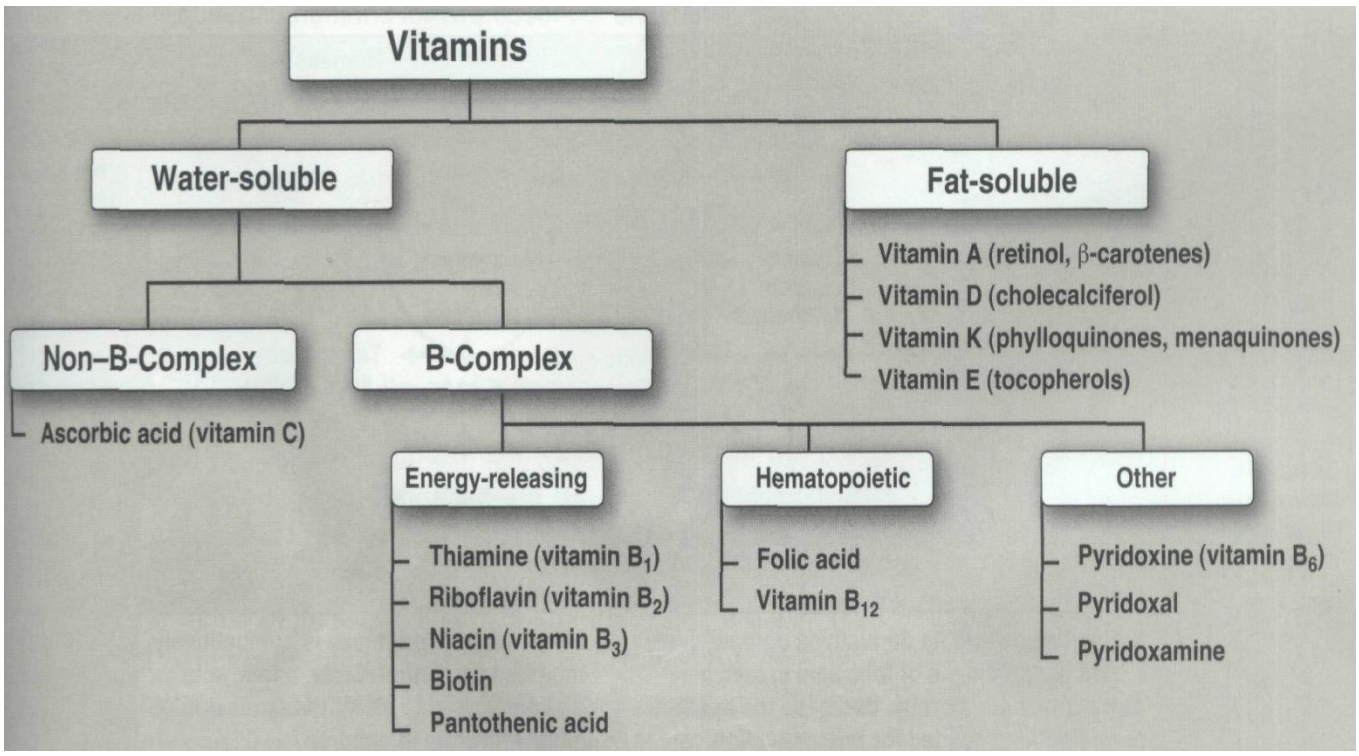
Vitamins

❖ **Definitions:**

- **Vitamins:** Are organic compounds that:
  1. **Essential** for many biochemical reactions.
  2. Many of them act as **coenzymes.**
  3. They **do not enter** in the structure of the tissues or **oxidized** by them.
  4. They are needed in **very small amounts.**
- **Provitamins:**
  - These are **precursors** of vitamins that converted into vitamins inside the body e.g. **carotenes** are **Provitamin A.**
- **Vitamers:**
  - These are different forms of one vitamin e.g. Vitamin **D** has **2 Vitamers**; D_2 and D_3.

❖ **CLASSIFICATION OF VITAMINS:** According to the solubility, vitamins are classified into:

- **A. Fat soluble vitamins:** These are vitamins: **A, D**, **E**, and **K**.
  1. They are **soluble** in **fat** solvents.
  2. They need **bile** salts for absorption.
  3. They can be **stored** in the body.
- **B. Water soluble vitamins:** These are vitamins: **C** and **B complex** group.
  1. They are **soluble** in **water**.
  2. Most of them are **not stored** in the body.

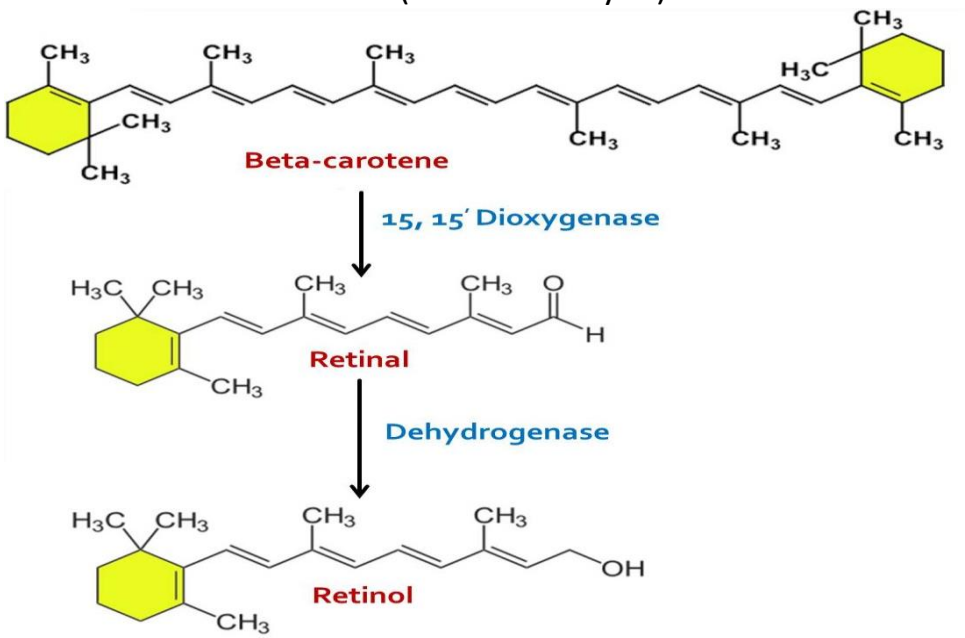


Fat soluble vitamins

VITAMIN A (retinoids)

Anti xerophthalmic

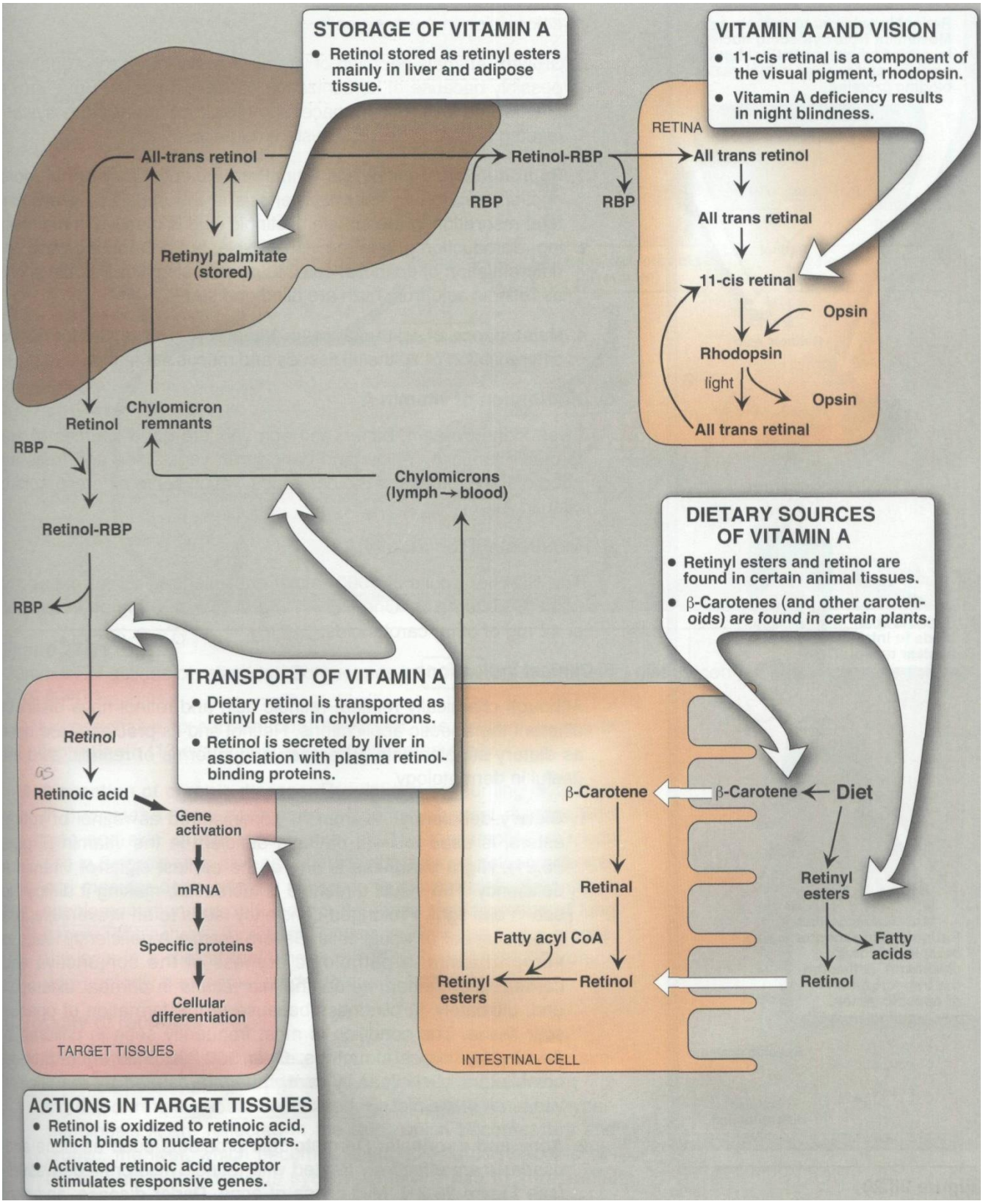
- **Structure:**
  1. **Carotenes** are the Provitamin **A**.
  2. **Retinol**, **retinal** and **retinoic acid** are the forms (**Vitamers**) used by the body.
- **Sources:**
  - **Animal sources:**
    a) Liver, eggs and milk fat. **b)** Fish liver oils e.g. shark liver oil.
  - **Plant sources:**
    a) Vitamin A is present in plants as (**carotenes**) (= Provitamin A).
    b) Carotenes (α, β and γ):
    1) Present in **carrots**, **potato** and **tomatoes**.
    2) Are **yellow pigments** containing **β-ionone ring** at one end of the molecule.
    3) Are converted into **vitamin A** (retinal aldehyde) in the **intestine**.



- **Metabolism:**
  - Diet contains **retinol esters** and **β-carotene**.
  - Retinol esters are hydrolyzed into **fatty acids** and **retinol** that absorbed into **intestinal mucosal** cells.
  - **β-carotene** is absorbed and converted into **retinal** (by **β-carotene** di-oxygenase enzyme). **Retinal** then converted into **retinol.**
  - In the intestinal mucosal cells, retinol **re-esterifies** with fatty acid to form **retinol ester.**
  - **Retinol esters** are absorbed through **lymph vessels** into general circulation and transported to the **liver**, where **90%** of the body's vitamin A is stored.
  - When the body cells need vitamin stored **retinol esters** are hydrolyzed and free retinol binds with a protein formed by the liver called **retinol binding protein RBP**). **BP** caries **retinol** to the **retina** and **target cells**.

a) In retina, retinols converted into retinal that **essential** for **vision**.

b) In other target cells retinol is **oxidized** into **retinoic acid** which binds to **nuclear receptors**. Retinoic acid receptor-complex stimulates **genes**. This mode of action is similar to hormones.



- **Functions of vitamin A:**

1. Vision

- Retinal is essential for **night vision**.

2. Reproduction:

- Retinol is essential for reproduction. It supports sperm formation **(spermatogenesis)** in **males** and **maintains fetal life** in **females**.

3. Growth:

- Retinol is essential for **normal growth** and **bone & teeth formation**.

4. Maintenance of epithelial cells:

- Retinol and retinoic acid are essential for **normal differentiation** of epithelial cells. This is important for **smoothness of skin** and **mucus membranes**.
- Retinol is also essential for **intact cornea**.

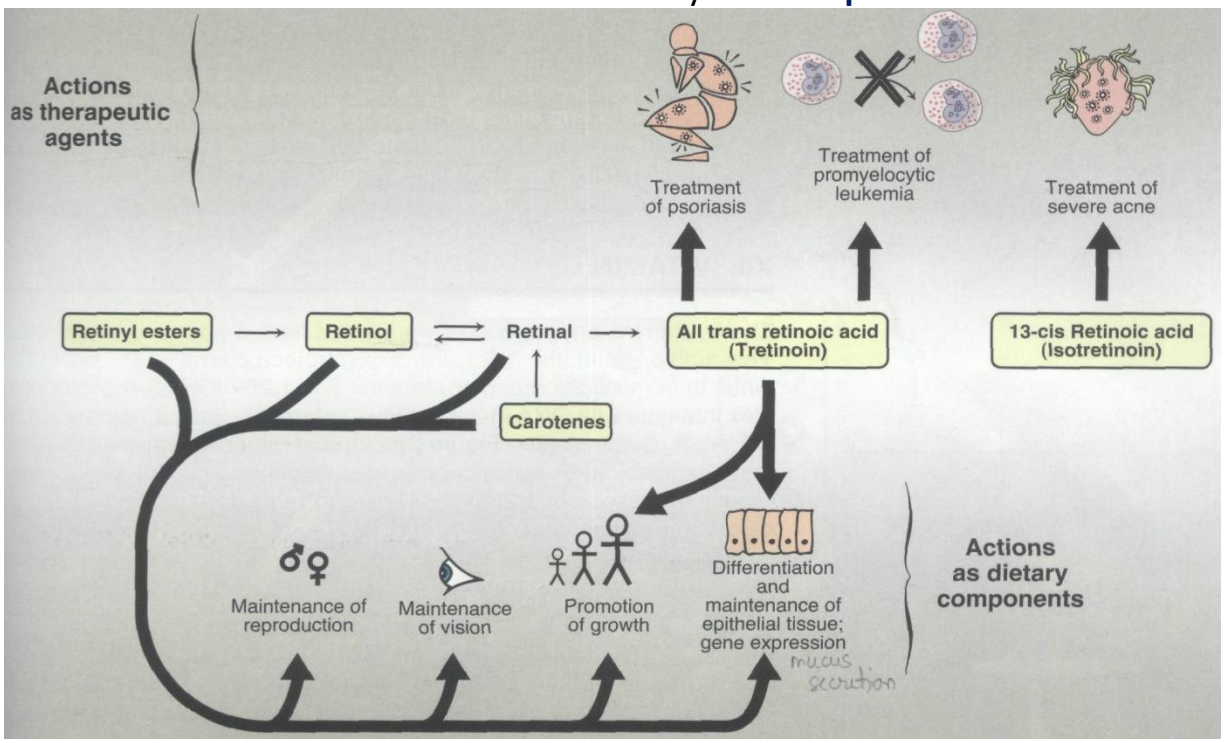
5. Retinoic acid: is important for

a) **Glycoprotein** synthesis.

b) **Phospholipids** synthesis in the lungs (**lung surfactant**).

6. Antioxidant (anticancer) action:

a) Retinoids and Carotenoids (**carotenes**) act as **antioxidants** and protect tissues from toxic effect of some **oxidants** that may lead to **epithelial tissue cancer.**



- **Vision:**

a) The human retina contains two types of receptor cells for vision; **cones** and **rods**:

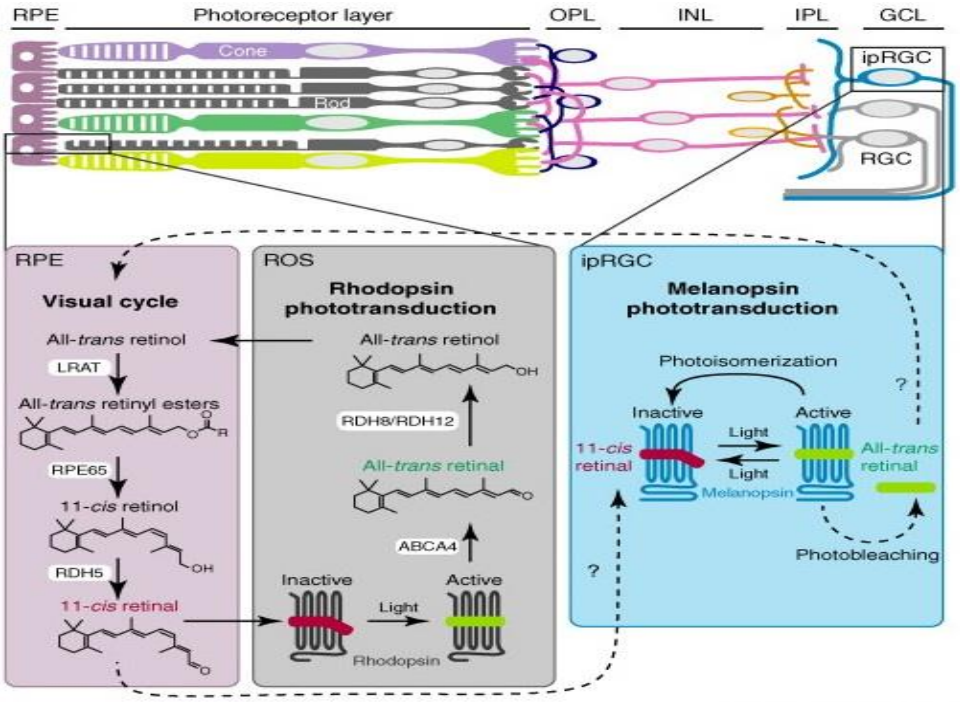
1) Cone cells are responsible for day vision and color.

2) Rod cells are responsible for vision in poor light e.g. at night.

b) Vitamin A is a component of a **visual pigment** (rhodopsin) present in **cones** and **rods**.

c) Visual cycle:

1) Rhodopsin consists of protein called opsin bound to 11-cis retinal (double bond at position 11 is in Cis form, while other double bonds are in Trans form).
2) When rhodopsin is exposed to dark light, 11 Cis retinal is converted into all Trans retinal (all double bonds are in Trans form).
3) All Trans retinal changes the permeability of cell membrane of rod cells. This allows the calcium ions to pass out of the cell membrane. This stimulates the nerve impulse in optic nerve. Thus the brain perceives light.
4) Rhodopsin must regenerate for vision. All Trans retinal are, converted back to 11-cis retinal. but this conversion is incomplete. This can be supplied from dietary retinol, which is oxidized to give 11-Cis retinal.



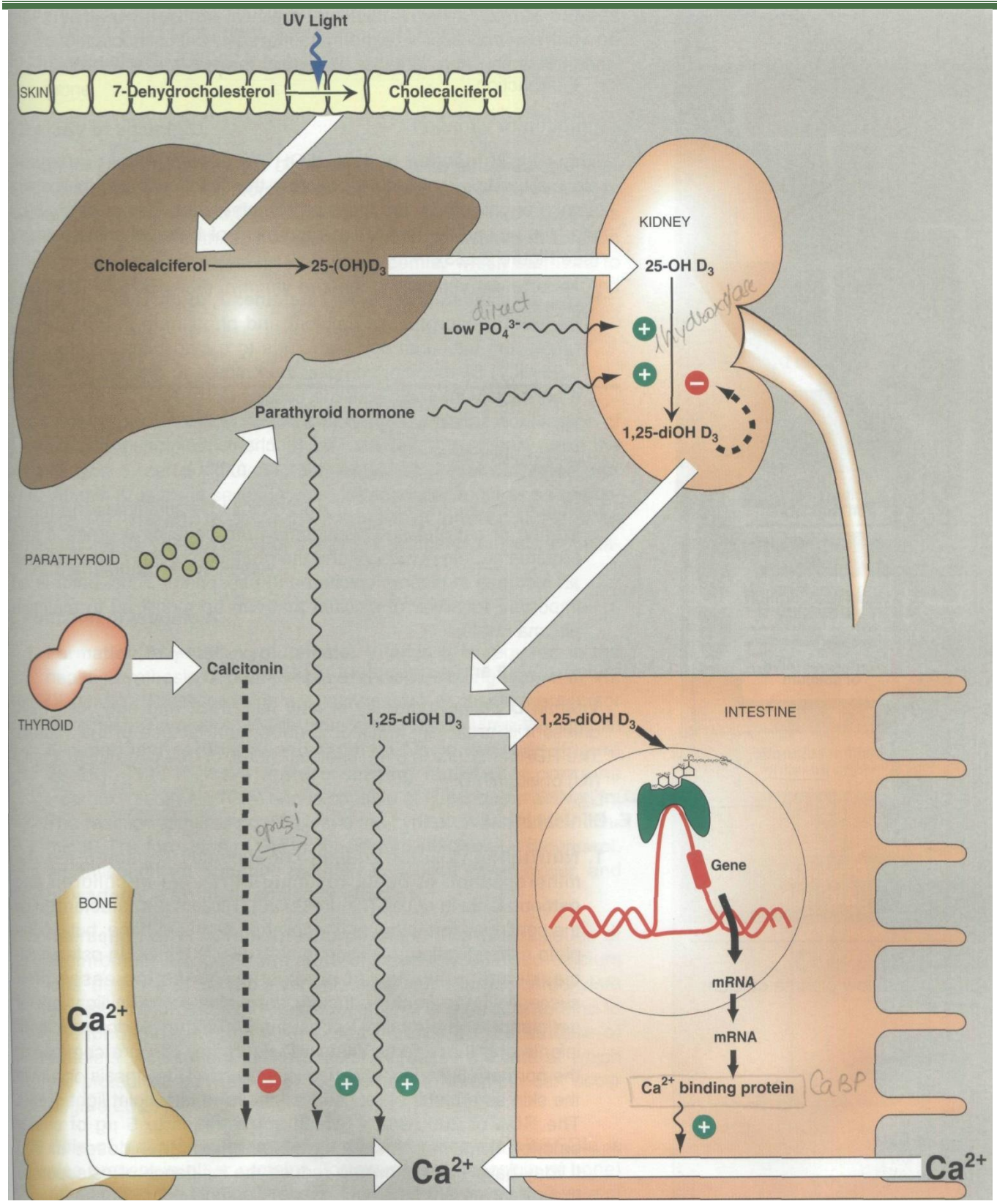
- **Deficiency of vitamin A:**
  1. **Eye:**
     - **Night blindness (Nyctalopia):** impaired dark adaptation.
     - **Xero-ophthalmia (Bitot spots):** dryness and roughness of cornea.
     - **Keratomalacia:** degradation of corneal epithelium.
     - **Blindness.**
  2. **Growth retardation.**
  3. **Skin and- mucus membranes:** Roughness of skin and mucus membranes of different body systems e.g. urinary system. This leads to infection.
  4. **Alopecia:** loss of hair from the head or body.
- **Requirements of vitamin A:** **5000 IU/day.**
- **Excess vitamin A (overdose):**
  - It occurs when excessive vitamin **A** intake exceeds the **capacity of RBP**.
  - Free retinol will release in blood with the following toxic effects:
  - **Headache** - **Nausea** - **Bone pain** - **Loss of hair.**

VITAMIN D (Calciferol)

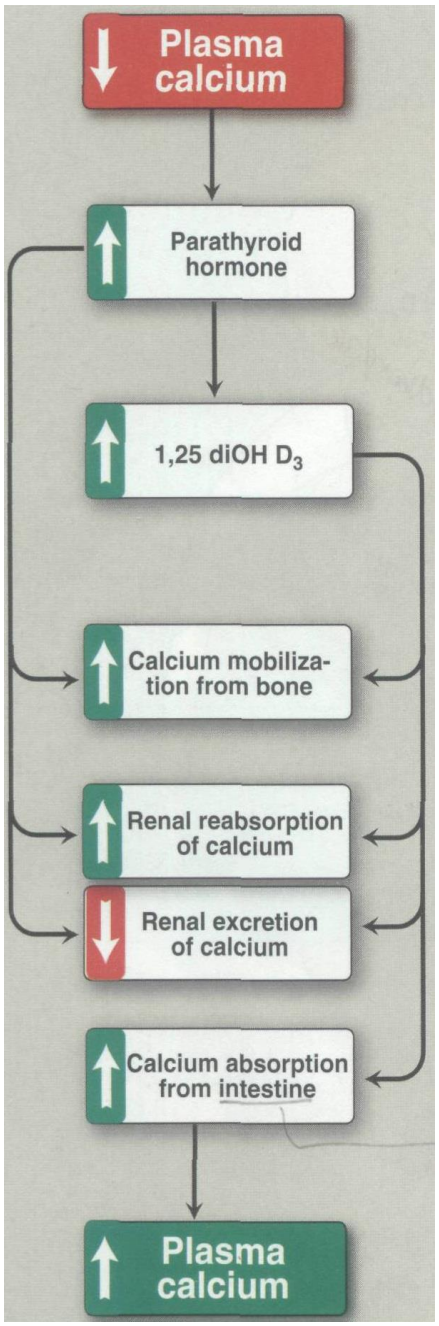
1, 25 dihydroxycholecalciferol

Calcitriol

- **Sources:**
  1. Ultraviolet rays of sun generate the D vitamins from the Provitamin ergosterol (in plants) and 7-dehydrocholesterol (in human and animals)
  2. Liver, egg, yeast and fish liver oils are rich in vitamin D.
- **Structure and activation of vitamin D group:**
  1. Active vitamin D is a steroid hormone. It is synthesized and activated as shown in the diagram.
- **Functions of vitamin D:** 1, 25 dihydroxycholecalciferol **(calcitriol)** acts as a hormone. It has the following functions:
  1. **Normalization of serum calcium (9-11 mg/dl):** Calcitriol maintains serum calcium level through its effects on **intestine**, **bones** and **kidneys**.
     - **a) On intestine:** it stimulates synthesis of calcium binding protein (**calbindin**) that responsible for calcium absorption.
     - **b) On bones:** It stimulates calcium resorption from bones.
     - **c) On kidneys:** It increases renal tubular reabsorption of calcium.
  2. **Mineralization of bones:**
     - **a) In small doses:** calcitriol helps bone mineralization by providing Ca^+ and p^+.
     - **b) In large doses:** The reverse occurs, where Ca^+ and p^+ move from bone to blood.
  3. **Absorption of phosphate from intestine:** It increases also tubular reabsorption of phosphate.
  4. **Synthesis of osteocalcin:**
     - It is calcium binding protein present in bones.
     - It is important for proper mineralization of bones.
     - **1, 25(OH)$_2$ D$_3$** stimulates its synthesis in the form of pro- osteocalcin.
     - **Note:** 24, 25 dihydroxycholecalciferol is biologically **inactive.**


UV Light
SKIN
7-Dehydrocholesterol
Cholecalciferol
Cholecalciferol
25-(OH)D3
KIDNEY
25-OH D3
direct
Low PO4 3-
hydroxylase
Parathyroid hormone
1,25-diOH D3
PARATHYROID
THYROID
Calcitonin
1,25-diOH D3
1,25-diOH D3
INTESTINE
opusi
Gene
BONE
Ca2+
mRNA
mRNA
Ca2+ binding protein
CaBP
Ca2+
Ca2+

- **Regulation and mechanism of action of 1,25 D^3 (calcitriol):**
  1. Hypocalcemia → release of parathyroid hormone → Activation of renal 1-hydroxylase enzyme → Conversion **25 (OH) D_3** into **1, 25$(OH)_2$ D_3**.
  2. Hypophosphatemia → Direct Activation of renal 1 hydroxylase enzyme → Conversion of **25 (OH) D_3** into **1, 25$(OH)_2$ D_3**.
  3. In the intestinal mucosal cells, **1, 25$(OH)_2$ D_3** is bound to specific cytoplasmic receptors forming a complex. This complex enters the nucleus, stimulating DNA to produce specific mRNA. This mRNA is responsible for synthesis of calcium binding protein (**calbindin**) which helps the absorption of calcium.
  4. Absorption of phosphate is similar to the previous mechanism but it occurs **secondary** to calcium absorption.
- **Deficiency of vitamin D:** Causes demineralization of bones that leads to rickets and Osteomalcia:
  - **Rickets in children:** characterized by bone deformities.
  - **Osteomalcia in adults:** characterized by bone fractures.
  - **Renal rickets:** In chronic renal failure there is a deficient formation of active form of the vitamin D_3 (decreased 1-hydroxylation of the vitamin). This leads to **renal rickets.**

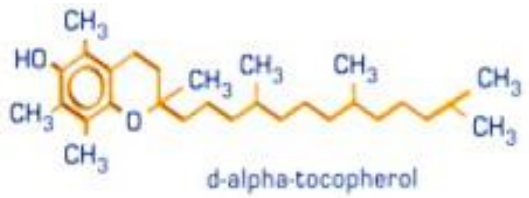


- **Requirements:** **400 IU/day.**
- **Excess vitamin D: (overdose or hypervitaminosis D):**
  This leads to abnormal calcification of tissues and deposition of calcium and phosphate in different systems e.g. **renal stones.**

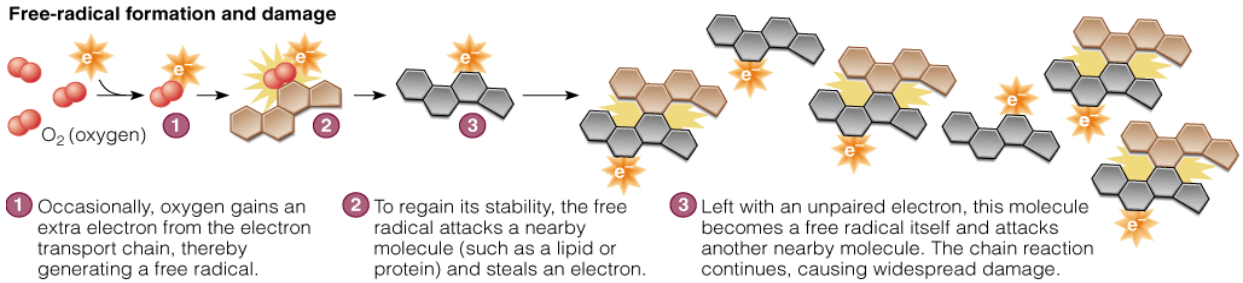
VITAMIN E (Tocopherols)

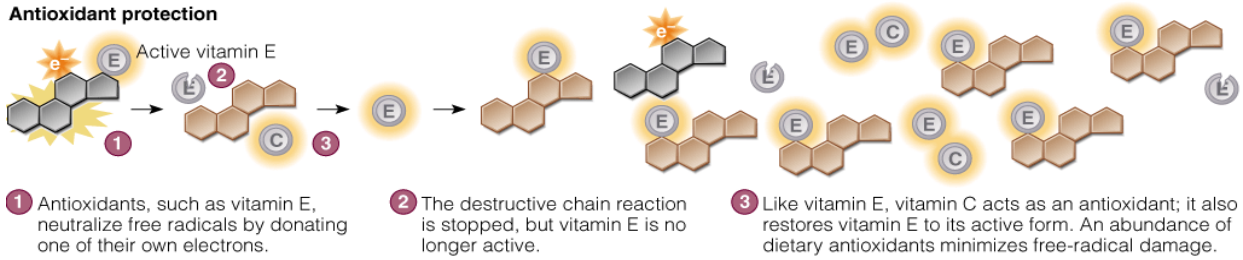
Tocotrienols

- **Structure**
  - There are **four types** of tocopherols **α, β, γ** and **δ**.
  - All contain **tocol** ring.
  - The most active member is **α tocopherol**.
  - **γ** and **δ** tocopherols differ from **α** tochopherol in number and position of **— CH_3** groups attached to the **tocol** ring.



- **Sources:** Vegetables and seed oils. It is present also in fish liver oils.
- **Functions of vitamin E:**
  1. **Antioxidant:** Vitamin E prevents non-enzymatic oxidation of cell components (e.g. polyunsaturated fatty acids, DNA and cell membranes) by molecular oxygen or free radicals.



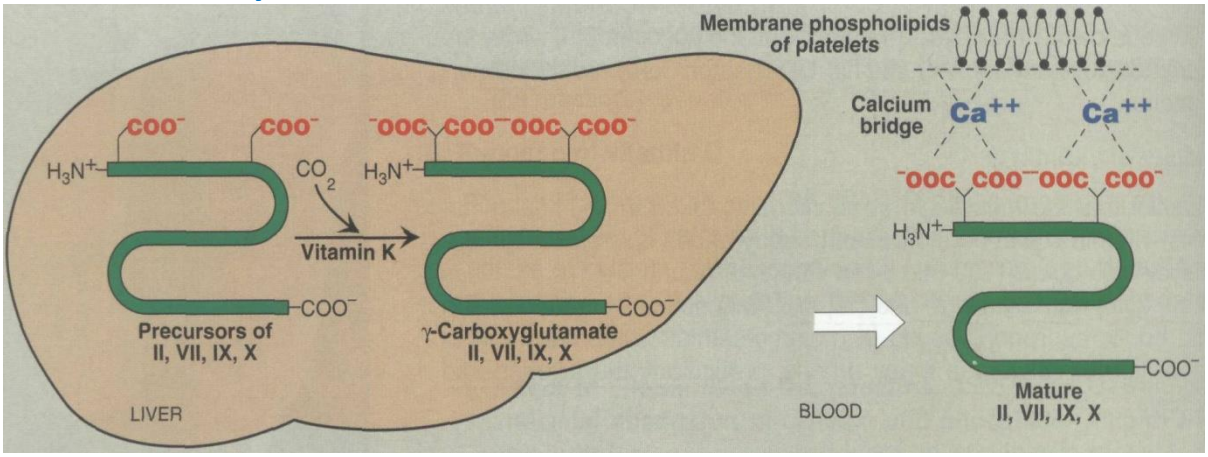


  2. **Vitamin E removes peroxide formation in polyunsaturated fatty acids.**
  3. **Protection against heart disease.**
     - Vitamin E acts as antioxidant. It prevents oxidation of **LDL**.
     - **Oxidized LDL** causes heart disease.
- **Deficiency:** Occurs usually in premature infant :
  1. Hemolysis of RBCs and anemia: due to lack of protection against peroxides.
  2. Muscle breakdown.
  3. Acanthocytosis (spiky RBCs).
  4. Peripheral neuritis.
  5. Ataxia: is a neurological sign consisting of lack of voluntary coordination of muscle movements.
  6. Retinitis pigmentosum.
- **Requirements:** **15 IU/day.**

VITAMIN K (anti hemorrhagic V)

Phylloquinone, menaquinone

- **Structure:** There are three forms (**Vitamers**) of vitamin K: K_1, K_2 and K_3.
  1. The difference between K_1 and K_2 lies in side chain R.
  2. K_3 is synthetic vitamin and has no R side chain.
- **Sources:**
  1. The main source of vitamin K is the intestinal bacteria. They produce Vitamin K_2
  2. Vitamin K_1 is present in plants.
  3. Vitamin K_3 is synthetic. It is water soluble and more potent than K_1 & K_2.
- **Functions of vitamin K :**
  1. Synthesis of some blood clotting factors in liver: prothrombin (factor II), and factors VII, IX and X (1972).
  2. Synthesis of **osteocalcin** (calcium binding protein) in bones.
- **Mechanism of action**
  - Prothrombin is a protein formed in the liver as inactive form called prothrombin precursor. It contains 10 glutamic acid residues.
  - Carboxylation of these glutamic acid residues into **γ-carboxy glutamate** converts the molecule into active thrombin.
  - The **same carboxylation** reactions occur to factors VII, IX and X.

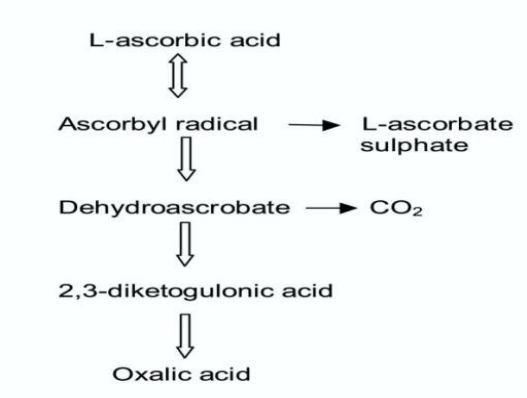


- **Deficiency of vitamin K:**
  - It leads to **impairment of blood clotting.**
  - Deficiency of **vitamin K** is rare because intestinal bacteria synthesize it.
  - Vitamin K deficiency occurs in the following conditions:
    a) **New born infant** because their intestine is **sterile**.
    b) **Prolonged** use of antibiotic as they **kill** intestinal bacteria.
    c) **Liver diseases:**
       1) Liver is the site for prothrombin synthesis.
       2) Liver forms bile salts which are essential for vitamin K absorption.
    d) **Prolonged** use of **Dicumarol** and **Warfarin** (anticoagulants) as they act as competitive inhibitors with vitamin K for its site of action.

Water Soluble Vitamins

VITAMIN C = (L-Ascorbic acid)

- **Sources:**
  - Fruits especially citrus fruits (lemon, orange), melon and strawberry.
  - Vegetables especially green leafy vegetables as lettuce, tomatoes, potatoes, raw cabbage and green peppers.
  - Guava is very rich in vitamin C.
- **Structure:**
  - Animal tissues contain **90%** L-ascorbic acid and **10%** dehydro L-ascorbic acid. Both forms are active.
  - Further oxidation gives inactive form called L-diketogulonic acid → oxalic acid.



- **Chemical properties:**
  - Ascorbic acid is acidic because it contains two enol groups (C-OH).
  - Vitamin C is the most labile vitamin in food i.e. easy to be destroyed. Much of its activity is lost through oxidation during preparation, cooking and storage.
- **Functions of vitamin C:**

1. **Formation of collagen protein:**
   a) Ascorbic acid is essential for the conversion of the Procollagen (immature collagen) into collagen. Procollagen is a protein containing proline and lysine. Hydroxylation of both amino acids is catalyzed by hydroxylase enzymes and by vitamin C as a **coenzyme**. This converts Procollagen into collagen.
   b) Collagen is essential for the synthesis of connective tissue, bone, cartilage and teeth.
2. **Absorption and mobilization of iron:** Ascorbic acid is a potent reducing agent, keeping iron in ferrous state:
3. **Acts as co-enzyme for many hydroxylase enzymes** in the pathway of:
   a) Bile acids synthesis: by 7 α hydroxylase.
   b) Osteocalcin synthesis: osteocalcin is calcium binding protein in bones.
   c) Carnitine synthesis: carnitine is a substance formed in the muscle. It stimulates fatty acid oxidation in mitochondria.
   d) Epinephrine synthesis: by hydroxylase required for conversion of tyrosine into epinephrine.
4. **Antioxidant action:** Vitamin C acts as antioxidant and protect tissues from toxic effect of some oxidants that may lead to cancer.

- **Deficiency:** → (**scurvy**):

- Vitamin C store is sufficient for 3 months. If this store is depleted a disease called scurvy will result. **It is characterized by:**

1. Manifestations due to decreased collagen formation:

a) Bleeding into gum, muscles, joints, kidneys, GIT and pericardium.
b) Defective formation of bone and teeth.
c) Defective healing of wounds.
d) Necrosis of gums and loss of teeth.

2. Anemia: due to decreased absorption of iron and bleeding.

3. Manifestations due to decreased neurotransmitters (epinephrine):

a) Behavioral changes.
b) Severe emotional disturbances.

4. Manifestations due to decrease carnitine and fatty acids oxidation:

a) General weakness.

- **Excessive vitamin C:**
  - Intake of high doses of vitamin C produces hyperoxaluria (increased oxalate in urine) and may lead to stone formation.
- **Requirements:**
  - 60 mg/day.

THE B COMPLEX VITAMINS

- **Introduction:**

A. These are a group of vitamins of different chemical molecules. They were put together in one group because:

1. All are soluble in water.
2. All are present in the same sources. B vitamins are particularly abundant in whole grain cereals, liver and yeast.
3. Due to their presence in the same foods: deficiencies of B vitamins are often multiple rather than singular.

- **Functions of vitamin B complex:**

1. All B-complex vitamins serve as coenzymes in enzymatic reactions.
2. Folic acid and B_{12} act as coenzymes in hematopoiesis (formation of red blood cells).

- **Absorption of vitamin B complex:**

1. The B vitamins are absorbed in the intestine and transported in the portal circulation.
2. The tissue stores of most B vitamins are minimal. The depletion occurs over several weeks in response to dietary restriction or increased the requirements as in pregnancy. Body stores of folic acid and vitamin B_{12} are more extensive than other B vitamins.

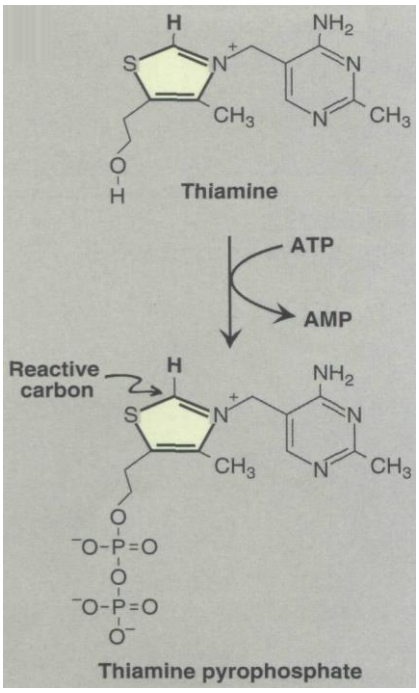
- **Toxicity of vitamin B complex:**
  - Toxic effects are relatively uncommon, since excessive ingestion of water soluble vitamins is followed by saturation of body stores and rapid loss of excess vitamins in the urine.

THIAMIN (vitamin B_1)

- **Sources:**
  1. Whole grain cereals legumes and yeast.
  2. Unpolished rice and whole wheat bread.
- **Structure:**
  1. Thiamin consists of a substituted pyrimidine ring connected to a substituted thiazole ring through a methylene bridge (**CH_2**)
  2. Active form of B_1 = Thiamin diphosphate (TPP):

  a) It is called also thiamin pyrophosphate.

  b) Formation of TPP needs thiamin kinase enzyme which is present in liver, red cells and nervous tissue.



- **Function**

  - TPP acts as coenzyme in two separate reactions in carbohydrate metabolism. These are:

  1. Oxidative decarboxylation of α- ketoacid: (pyruvate, α-Ketoglutarate and ketoacids of branched chain amino acids; Valine, Leucine and Isoleucine) by:

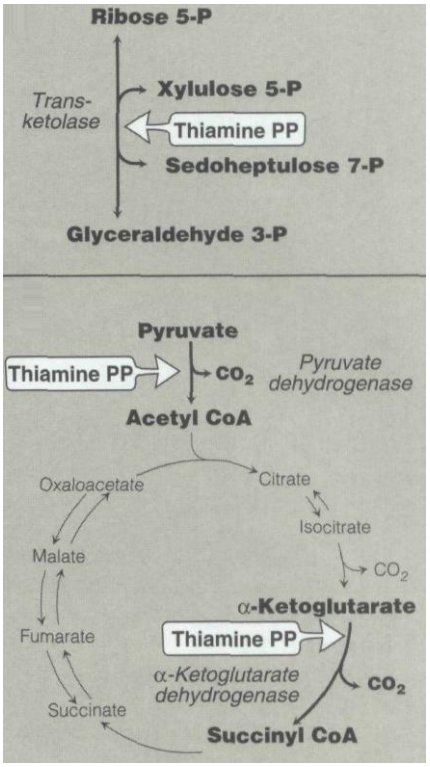
  a) Pyruvate dehydrogenase enzyme.

  b) α-Ketoglutarate dehydrogenase (in citric acid cycle, CAC).

  - **Note:** These reactions produce energy and CO_2.

  2. Transketolation reactions: by transketolase, in **pentose phosphate pathway**.

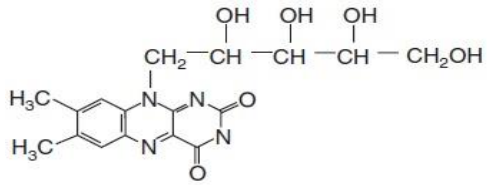
  3. Thiamin is also essential for the process of **nerve conduction** and **structure of nerve membrane.** Thiamin triphosphate acts as phosphate donor for phosphorylation of sodium transport channel of the nerve membrane.



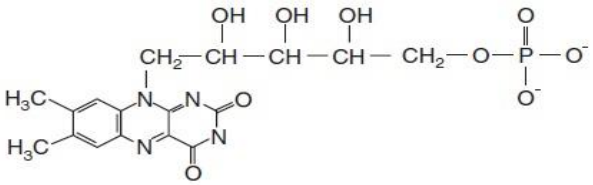
- **Deficiency:** **Beriberi** (Wernicke-Korsakoff syndrome)
  1. ↓TPP → impaired conversion of pyruvate to acetyl CoA this leads to ↓ Energy production → Impaired cellular functions epecially of nervous system → beriberi
  2. **Types of beriberi:**
     - **a) Acute beriberi** (also called dry beriberi) characterized by:
       1. Peripheral neuritis (numbness).
       2. Muscle wasting (paralysis of the lower legs).
       3. Mental confusion/speech difficulties.
     - **b) Chronic beriberi:** (also called wet beriberi) characterized by:
       1. Heart failure.
       2. Edema.
       3. Dyspnea on exertion.
     - **c) Infantile beriberi**
       - This type of beriberi is commonly found in children in developing countries. Obvious signs and symptoms are crying, but not loudly and without tears. Untreated, it can prove fatal within 24 hours.
- **Requirements:** **1.5 mg / day.**

RIBOFLAVIN (vitamin B_2)

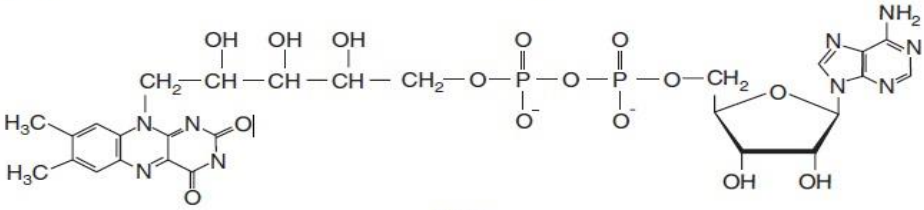
- **Sources:**
  1. Milk and milk products
  2. Eggs, liver and green leafy vegetables.
- **Structure:**
  1. It is formed of Flavin ring attached to ribitol (alcohol of ribose sugar).
  2. **Active forms of riboflavin.**
     - **a)** Riboflavin enters in the structure of Flavin mononucleotide (FMN) and Flavin adenine dinucleotide (FAD)
     - **b)** FMN is formed by phosphorylation of riboflavin by ATP (by intestinal flaviokinase enzyme).
     - FAD is formed by the transfer of an AMP moiety from ATP to FMN.



Riboflavin



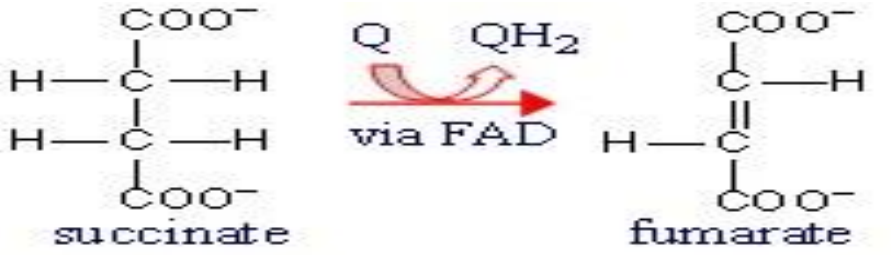
FMN



FAD

- **Functions of B_2:**
  1. Both FMN and FAD are coenzyme for flavor-enzymes. They act as hydrogen (or electron) carriers in oxidation reduction reactions → $FMNH_2$ and $FADH_2$.
  2.

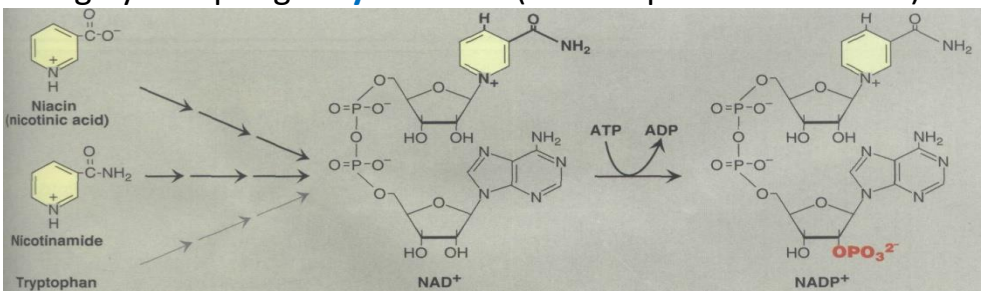
- **Examples:**



- **Deficiency:** B_2 deficiency is **not** fatal. It is characterized by:
  1. **Ocular disturbances:**
     a) Photophobia i.e. abnormal sensitiveness of the eye to the light.
     b) Vascularization of cornea.
  2. **Cheilosis** (fissuring at the corners of the mouth).
  3. **Glossitis** i.e. inflammation of tongue, which appears smooth and purplish.
  4. **Dermatitis** i.e. inflammation of the skin.
- **Requirements:** **1.5 mg/day.**

NIACIN (nicotinic acid, B_3)

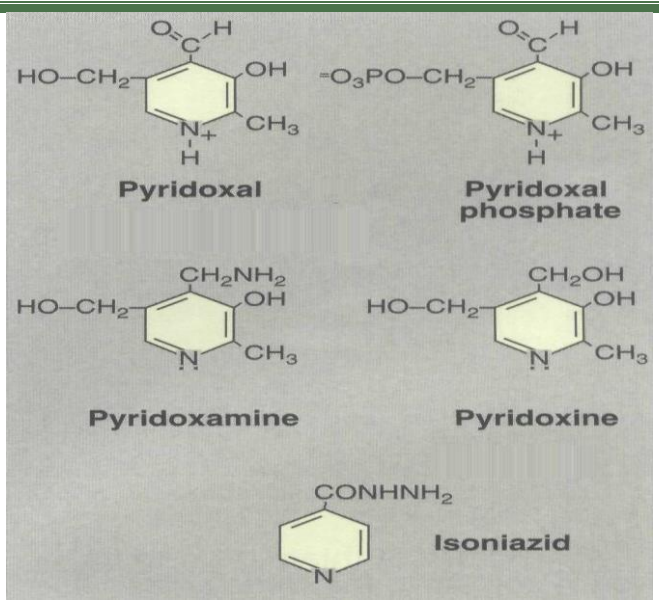
- **Sources:**
  1. Whole grain and cereals.
  2. Milk, meat, liver, and yeast.
  3. Niacin can be synthesized endogenously from the amino acid **tryptophan:**
     a) Each **60 mg tryptophan** can be converted to **1 mg niacin**. This conversion requires vitamin **B6**, as a co-enzyme.
     b) **Meat** is rich in tryptophan, so it is important source of niacin.
     c) Corn is poor in both niacin and tryptophan.
- **Structure:**
  1. Niacin (nicotinic acid) is a pyridine derivative.
  2. It is a nontoxic substance present in a toxic alkaloid nicotine of tobacco.
  3. **Active forms:**
     a) Niacin is converted to the active form Nicotinamide that enters in the structure of Nicotinamide adenine dinucleotide (**NAD**) and Nicotinamide adenine dinucleotide phosphate (**NADP**).
     b) Nicotinamide, a derivative of nicotinic acid contains **amide** group.
- **Synthesis of NAD and NADP:**
  - The formation of **NAD** and **NADP** occurs in **cytosol** of **liver** cells. NADP has similar structure in addition to phosphate.
  - NAD and NADP present in two forms **oxidized** and **reduced**. They undergo reduction of pyridine ring by accepting a **Hydride ion** (H atom plus one electron).



- **Functions of niacin:**
  1. **Formation of (NAD) and (NADP):**
     - These two coenzymes function as hydrogen carriers and they are essential for many biochemical oxidation-reduction reactions.
     - These reactions are important in carbohydrate, protein and lipid metabolism.
  2. **Lowering plasma cholesterol.** Niacin can be used in treatment of high plasma cholesterol and lipids. Niacin lowers plasma cholesterol concentration. This is due to inhibition of flow of free fatty acids (FFA) from adipose tissue which provides acetyl CoA molecules essential for cholesterol and triacylglycerols synthesis.
  3. **Formation of ADP-ribose:** NAD^+ is a source of **ADP-ribose**: It is important for:
     a) ADP-ribosylation of protein.
     b) Poly ADP ribosylation of nucleoproteins involved in DNA repair mechanism.
- **Deficiency:** **pellagra**
  - Deficiency of niacin causes pellagra, a disease affects the **skin**, **GIT** and **CNS**.
  - **Manifestation of pellagra:**
  - Pellagra is called a disease of (**4 Ds**): **diarrhea**, **dermatitis**, **dementia** and if not treated **death**.
  - **Causes:**
    a) Deficiency of **niacin**, **tryptophan** or vitamin **B_6**.
    b) Corn is deficient in both niacin and tryptophan. Thus people who depend on corn as a major source of protein as some farmers develop pellagra.
    c) **Hartnup's disease:** It is a hereditary disease in which here is defect in tryptophan absorption form intestine and tryptophan reabsorption by renal tubules → Pellagra.
    d) **Argentaffinoma** (malignant carcinoid syndrome): In which large quantities of tryptophan is converted to serotonin. This occurs on the expense of niacin synthesis → pellagra.
    e) **Isoniazid:** it is a drug that is used in treatment of **tuberculosis**. Isoniazid binds with B_6 → Excretion by kidney → pellagra.
- **Requirements:** Niacin **20 mg / day.**
- **Hypervitaminosis of niacin:**
  - More than **500 mg/day** may cause **liver damage.**

PYRIDOXINE (vitamin B_6)

- **Sources:** wheat, egg yolk, corn, liver and meat.
- **Structure:**
  1. Vitamin B_6 includes a group of Vitamers derived from pyridine ring.
  2. These are pyridoxine, pyridoxal and pyridoxamine.
     - They differ in the, nature of functional group attached to the ring.
     - All 3 compounds can act as precursors of the biologically active co-enzyme Pyridoxal phosphate **(PLP).**



- **Functions:**

- In the body, pyridoxine is converted to pyridoxal phosphate, which acts as a coenzyme for a large number of enzymes:

A. In protein metabolism:

It acts as a coenzyme for amino acids metabolism in the following reactions:

1) Transamination e.g.

Glutamate + Oxaloacetate ↔ α-Ketoglutarate + Aspartate

2) Trans-sulfuration e.g.

Methionine → Homocysteine (+ serine) → Cysteine + Homoserine.

3) Deamination e.g.

Serine → Pyruvate + NH_3

4) Decarboxylation e.g.

Glutamate → GABA + CO_2

5) Heme synthesis e.g.

Glycine + Succinyl CoA → δ Aminolevulinic acid → Heme.

6) Pyridoxal phosphate acts as a coenzyme in conversion of tryptophan into vitamin B_3 (niacin).

7) Sphingosine synthesis: Serine + Palmitate

8) It takes a role in amino acids absorption from the **intestine**.

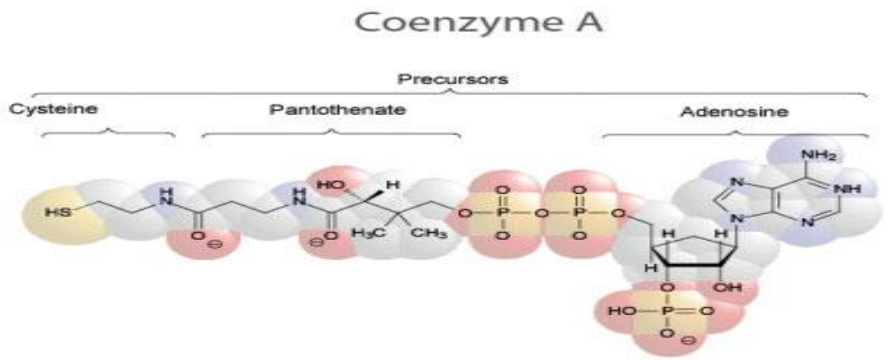
B. In carbohydrate metabolism: Pyridoxal phosphate acts as a coenzyme of **glycogen Phosphorylase** → Glycogen breakdown into glucose (glycogenolysis).

C. In lipids metabolism: Pyridoxal phosphate is important in steroid hormone action, where it **removes the hormone- receptor complex from DNA binding**, terminating the action of hormone.

- **Deficiency:**
  1. **Pellagra** may result, because pyridoxal phosphate is needed for the conversion of tryptophan into vitamin B_3 (niacin).
  2. **Convulsions in young infants** due to deficient formation of GABA (inhibitory transmitter in brain).
  3. **Anemia** (microcytic and hypochromic) due to deficient formation of heme and hemoglobin.
  4. **Disturbance in amino acids metabolism**. This leads to growth retardation and may be mental retardation.
  5. **Cancer breast**, **uterus** and **prostate:** due to defective action of B_6 on steroid DNA binding.
  6. **Homocystenuria:** It is due to inability to convert Methionine to cysteine.
- **Hypervitaminosis of B_6:**
  - Intake of more than 200 mg/day B_6 may cause neurological damage.
- **Requirements:** **2 mg / day.**

PANTOTHENIC ACID

- **Sources:**
  - Animal tissue as meat, liver, kidney.
  - Legumes.
- **Structure:**
  - Pantothenic acid is formed of pantoic acid (α and γ dihydroxy β dimethyl butyric acid) connected to β-alanine.
- **Functions:**
  1. **Coenzyme A (CoASH):**
     a) Structure: is formed of phosphopantotheine (= phosphate + pantothenic acid + Thioethylamine) attached to biphosphoadenosine.
     b) Function:
     - Coenzyme A acts in the transfer of acyl groups e.g. acetyl CoA, Succinyl CoA, malonyl CoA and other carboxylic acids.
       1) **Acetyl CoA:** It is an important intermediate in metabolism of carbohydrate, lipids and protein metabolism.
       2) **Succinyl CoA:** used in heme synthesis and other reactions.
       3) **Malonyl CoA:** is used in fatty acid synthesis.



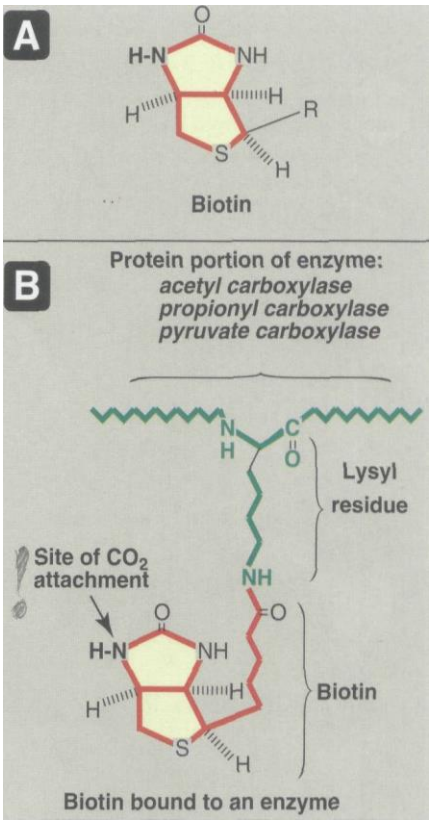
2. Acyl carrier protein (ACP):

a) Structure: ACP is formed of: Pantothenic acid connected to phosphate and protein in one side and Thioethylamine in the other side.

b) Functions: ACP is a component of fatty acid synthase enzyme required for fatty acid synthesis.

- **Deficiency:** Deficiency of pantothenic acid causes no effect in human.
- **Requirements:** **5 - 10 mg / day.**

BIOTIN



- **Sources:**
  1. The **intestinal bacteria** synthesize most of the human requirements of biotin.
  2. Egg yolk, animal tissues, tomatoes and yeast are excellent sources.
- **Structure:**
  - Biotin consists of thiophen ring connected to urea with Valeric acid as side chain
  - Biotin acts as CO_2 carrier. It attaches to carboxylase enzyme (through the ε amino group of lysine residues to form biocytin a reaction catalyzed by holocarboxylase synthetase enzyme.
  - Deficiency of such enzyme may lead to deficiency manifestation of biotin.
  - CO_2 is attached to N of biotin to form CO_2 biotin enzyme complex.

  The CO_2 group is then transferred to the substrate for carboxvlation.

  carboxylation reactions.
  - Example of important carboxylation reactions are:
    1. Carboxylation of acetyl CoA to malonyl CoA:
       Is important reaction in fatty acid synthesis.
    2. Carboxylation of pyruvate to oxaloacetate:
       Is important reaction in Gluconeogenesis.
    3. Carboxylation of Propionyl CoA to give Succinyl CoA.

  B. **Regulation of cell cycle:** Biotin also has a role in regulation of cell cycle.
- **Deficiency:**
  1. Deficiency of biotin does not occur in man because:
     - The intestinal bacteria supply all the human needs.
     - Biotin is widely distributed in food.
  2. **Biotin deficiency may result from:**
     a) Ingestion avidin: it is a glycoprotein present in uncooked egg white. It tightly binds biotin and prevents its absorption from the intestine.

b) Deficiency of holocarboxylase synthetase enzyme in children. This enzyme is responsible for the attachment of biotin to carboxylase enzyme.

3. The manifestations biotin deficiency **include:**
   Muscle pain, dermatitis, Glossitis, loss of appetite and nausea.

2. The requirements increase during late pregnancy and lactation.

CHOLINE

- Choline is sometimes not regarded as a vitamin because:
  1. It is needed in a relatively big amount.
  2. It can be formed in the body from serine.
  3. It enters in structure of tissues.

- **Physiological function:**
  1. It enters in the formation of lecithin and Sphingomyelin.
  2. It has a lipotropic action. i.e. it prevents fatty liver.
  3. It enters in the formation of acetylcholine.
  4. Oxidation of Choline produces betaine. Betaine functions as a methyl donor in Transmethylation reactions.

INOSITOL

- **Structure:** It is sugar alcohol derived from glucose.
- **Physiological functions:**
  1. It enters in the structure of Phosphatidyl Inositol, which act as lipotropic factor.
  2. Inositol triphosphate (IP) acts as a second hormone messenger (see mode of action of hormones).

- Note: Inositol can combine with 6 molecules of phosphoric acid to form Phytic acid. Phytic acid combines with Ca^{2+} ions to form Ca^{2+} phytate which is insoluble in water. So, the presence of phytic acid in food decreases Ca^{2+} absorption.

LIPOIC ACID

- **Structure:**
  It is 6-8 dithio-ocatnic acid (8C)
- **Physiological functions:**
  - It acts as coenzyme in oxidative decarboxylation of α-Keto acids e.g. pyruvic acid

References:

1- Harper's 30th edition

2- Lippincott

3- First Aid 2018

4- Kaplan Biochemistry

5- BRS biochemistry